Oxygen debt in critically ill patients

Monitoring and additionals

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Introduction

Shock is defined as global tissue hypoxia secondary to an imbalance between systemic oxygen delivery (DO_2) and oxygen demand (VO_2). Unrecognized and untreated global tissue hypoxia increases morbidity and mortality. Accurate detection of global tissue hypoxia is therefore of vital importance. Physical findings, vital signs, measuring central venous pressure (CVP) and urinary output are important, but insufficient for accurate detection of global tissue hypoxia [1-3]. Measurement of mixed venous oxygen saturation (SvO_2) from the pulmonary artery (PA) has been advocated as an indirect index of tissue oxygenation [4]. However, as a result of an extensive debate in literature [5-7], the use of the pulmonary artery catheter (PAC) has become, justifiable or not [8], somewhat unpopular. In contrast, insertion of a central venous catheter in the superior vena cava via the jugular or subclavian vein is considered standard care in critically ill patients. Just as SvO_2, the measurement of central venous oxygen saturation ($ScvO_2$) has been advocated as a derivative of global tissue hypoxia. Venous oxygen saturations have been subject of research for over fifty years, but especially over the last decade the amount of literature describing changes in $ScvO_2$ and SvO_2 in critically ill patients increased substantially.

The main reason for the revival of interest in venous oxygen saturations was the publication of the so-called Early Goal-Directed Therapy (EGDT) study by Rivers *et al* [9]. In this study an impressive mortality reduction was achieved in favour of the patients treated according to the EGDT protocol which included $ScvO_2$-guided therapy. This led to high expectations with respect to the use of central venous oxygen saturation as a therapeutic goal. In a strict sense the goal would be a $ScvO_2$ value ≥70% which deems a lower $ScvO_2$ at patient presentation. After a literature search on the clinical use of venous oxygen saturations in various settings, chapter 2 describes the occurrence of low $ScvO_2$ and SvO_2 values in 340 critically ill patients at intensive care unit (ICU) admittance. Central question: is EGDT still commonly indicated as suggested by the Surviving Sepsis Campaign Guidelines [10], if a minority of septic patients reveals low venous oxygen saturations?

The PAC, together with the defining variables it provides including SvO_2, has been a fundamental hemodynamic monitoring tool in ICUs for over 40 years. Consequently, replacement of SvO_2 by $ScvO_2$ in diagnostic and therapeutic strategies asks not only for arguments but also for nuance. In other words, are both values equal or interchangeable, in septic shock especially, and is this clinically relevant? In chapter 3 the generally adopted difference of 5% between SvO_2 and $ScvO_2$ is addressed [11-13], also paying attention to the question on the use of both variables in patients with septic shock.

In clinical practice, when insertion of a central venous catheter in the superior vena cava via the jugular or subclavian vein is impossible, the alternative central venous access is the femoral vein. Unfortunately, monitoring $ScvO_2$ is then out of the question. However, as shown in a recent survey, femoral venous oxygen saturation ($SfvO_2$) is used during the first hours of treatment [14]. Femoral access is quick and relatively safe and potentially very useful in the care of acutely ill patients, especially if $SfvO_2$ would provide diagnostic information in accordance with $ScvO_2$. The question whether $SfvO_2$ is such an attractive alternative is addressed in chapter 4. In 3 different populations the statistical agreement is described: stable cardiac outpatients, patients undergoing high-risk surgery, and critically ill ICU patients.

Venous oxygen saturations are the best surrogates for global tissue hypoxia at this point and when used appropriately they are both useful diagnostic tools and of prognostic value. However, venous oxygen saturations do not have the exclusive right to these entitlements, because lactate has to be considered too. This product of metabolism, i.e. glycolysis, has been monitored in ICUs for many years. It is known that in anaerobic conditions lactate concentrations increases. As a consequence hyperlactataemia may serve as a marker for tissue hypoxia as well. But the pathophysiology of hyperlactataemia is complex and the meaning of hyperlactataemia in critically ill patients remains under debate [15,16]. This controversy includes the use of lactate as a marker of hypoxia [17].

Nevertheless, the prognostic value of lactate in this context has not been questioned as extensively.

Clinical application of point-of-care measurements of arterial blood gas, glucose and lactate has been spread over the years in the emergency department (ED), operating room (OR) and ICU. With the introduction of hand held lactate metres it became possible to measure lactate outside these facilities or even outside the hospital. In chapter 5, the results are reported of a feasibility study on the use of such hand held metres in a prehospital setting. We compared the prognostic value of lactate with the prognostic value of vital signs in both shock and non-shock patients. This is relevant because if lactate would outperform vital signs, in non-shock patients especially, then lactate could be added to the current diagnostic pallet available to paramedics.

In a later stage, i.e. after ICU admittance, persistence of hyperlactataemia could be a sign of on-going disease without apparent improvement. Hyperlactataemia is associated with multiple organ dysfunction syndrome (MODS) [18-21], which in turn influences the outcome of the septic patient [10]. Additionally, persistence of lactate levels above normal is associated with higher mortality rates in patients with severe sepsis or septic shock [20,22,23]. Therefore, it is possible that duration of hyperlactataemia outperforms single lactate measurements in predicting outcome. In chapter 6 the relationship between hyperlactataemia and organ failure as described by the Sequential Organ Failure Assessment (SOFA) is described in an ICU population of 2251 patients [24-26], in particular in relation to final outcome.

Both $ScvO_2$ and lactate are, to a greater or lesser extent, a reflection of a possible oxygen debt in critically ill patients. Above that, both values have been used in a diagnostic and therapeutic manner. However, normal values do not guarantee adequate tissue oxygenation and other circulatory parameters are needed to evaluate either treatment with catecholamines or resuscitation efforts altogether. One parameter that has been described in

this context is the central venous-to-arterial carbon dioxide difference (pCO_2 gap) [27]. The pCO_2 gap reflects adequacy of blood flow [28,29], i.e. cardiac output (CO). CO, combined with other variables such as vital signs and $ScvO_2$, gives us an idea on cardiac performance and physiological reserve of the patient. Hence, the pCO_2 gap may be of additional value during resuscitation of critically ill patients. The final chapter of this thesis explores the place of the pCO_2 gap in the resuscitation of patients with severe sepsis or septic shock during the first 24 hours after ICU admittance.

References

1. Rady MY, Rivers EP, Novak RM: **Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate.** *Am J Emerg Med* 1996, **14**:218-225.
2. Wo CC, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E: **Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness.** *Critical Care Medicine* 1993, **21**: 218-223.
3. Vincent JL, De Backer D: **Oxygen uptake/oxygen supply dependency: fact or fiction?** *Acta Anaesthesiol Scand Suppl* 1995, **107**:229-237.
4. Kandel G, Aberman: **A Mixed venous oxygen saturation: its role in the assessment of the critically ill patient.** *Arch Int Med* 1983, **143**: 1400-1402.
5. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell Jr FE, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson Jr WJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA: **The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT investigators**. *JAMA* 1996, **276**: 889-897.
6. Sakr Y, Vincent JL, Reinhart K, Payen D, Wiedermann CJ, Zandstra DF, Sprung CL: **Use of the pulmonary catheter is not associated with worse outcome in the ICU**. *Chest* 2005, **128**: 2722-2731.
7. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, Rowan K: **Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial.** *Lancet* 2005, **366**: 472-477.
8. Vincent JL: **So we use less pulmonary artery catheters – But why?** *Crit Care Med* 2011; **39**: 1820-1822.
9. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; for the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**:1368-1377.
10. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, marshall J, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; for

Surviving Sepsis Campaign: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**:858-873.

11. Varpula M, Karlsson S, Ruokonen E, Pettilä V: **Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock**. *Intensive Care Med* 2006, **32**:1336-1343.
12. Chawla LS, Zia H, Guttierez G, Katz NM, Seneff MG, Shah M: **Lack of equivalence between central and mixed venous oxygen saturation**. *Chest* 2004, **126**:1891-1896.
13. Rivers E: **Mixed vs central venous oxygen saturation may be not numerically equal, but both are still clinically useful**. *Chest* 2006, **129**:507-508.
14. Davison DL, Chawla LS, Selassie L, Jones EM, McHone KC, Vota AR, Junker C, Sateri S, Seneff MG: **Femoral-based central venous oxygen saturation is not a reliable substitute for subclavian/internal jugular-based central venous oxygen saturation in patients who are critically ill.** *Chest* 2010; **138**: 76-83.
15. Levy MM, Macias WL, Vincent JL, Russell JA, Silva E, Trzakoma B, Williams MD: **Early changes in organ function predict eventual survival in severe sepsis.** *Crit Care Med* 2005, **33**: 2194-2201.
16. Gutierrez G, Williams JD: **The riddle of hyperlactataemia**. *Crit Care* 2009, **13**: 176.
17. Bellomo R, Reade MC, Warrilow SJ: **The persuit of a high central venous oxygen saturation in sepsis: growing concerns.** *Crit Care* 2008, **12**: 130.
18. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry Sm, Greenspan J: **Lactate clearance and survival following injury.** *J Trauma* 1993, **35**: 584-589.
19. Donati A, Cornacchini O, Loggi S, Caporelli S, Conti G, Falcetta S, Alò F, Pagliariccio G, Bruni E, Preiser JC, Pelaia P: **A comparison among portal lactate, intramucosal sigmoid pH, and deltaCO2 (PaCO2 – regional Pco2) as indices of complications in patients undergoing abdominal aortic aneurysm surgery.** *Anesth Analg* **2004**, 99: 1024-1031.
20. Callaway DW, Shapiro NI, Donnino MW, Baker C, Rosen CL: **Serum lactate and base deficit as predictors of mortality in normotensive elederly blunt trauma patients**. *J Trauma* 2009, **66**: 1040-1044.

21. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL: **Serial blood lactate levels can predict the development of multiple organ failure following septic shock**. *Am J Surg* 1996, **171**: 221-226.

22. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL: **Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock.** *Chest* 1991, **99**: 956-962.

23. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC: **Early lactate clearance is associated with improved outcome in severe sepsis and septic shock**. *Crit Care Med* 2004, **32**: 1637-1642.

24. Peres Bota D, Melot C, Lopes Ferreira F, Nguyen Ba V, Vincent JL: **The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction.** *Intensive Care Med* 2002, **28**: 1619-1624.

25. Cabré L, Mancebo J, Solsona JF, Saura P, Gich I, Blanch L, Carrasco G, Martín, Bioethics Working Group of the SEMICYUC: **Multicenter study of the multiple organ dysfunction syndrome in intensive care units - the usefulness of the Sequential Organ Failure Assessment scores in decision making**. *Intensive Care Med* 2005, **31**: 927-93.

26. Vincent JL, de Mendonca A, Cantraune F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S: **Use of the SOFA score to assess the incidence of organ system dysfunction/failure in intensive care units: results of a multi-center, prospective study**. *Crit Care Med* 1998, **26**: 1793-1800.

27. Vallée F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii, Fourcade O, Genestal: **Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock?** *Intensive Care Med* 2008, **34**: 2218-2225.

28. Johnson BA, Weil MH: **Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses**. *Crit Care Med* 1991, **19**: 1432-1438.

29. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI: **Difference in acid-based state between venous and arterial blood during cardiopulmonary resuscitation**. *N Engl J Med* 1986, **315**: 153-156.

Chapter 1

The use of venous oxygen saturations as a goal:

a yet unfinished puzzle

A clinical review

Paul van Beest, Götz Wietasch,

Thomas Scheeren, Peter Spronk, Michaël Kuiper

Abstract

Shock is defined as global tissue hypoxia secondary to an imbalance between systemic oxygen delivery and oxygen demand. Venous oxygen saturations represent this relationship between oxygen delivery and oxygen demand and can therefore be used as additional parameter to detect an impaired cardiorespiratory reserve. However, before appropriate use of venous oxygen saturations one should be aware of its physiology. This article describes the physiology of venous oxygen saturations and the use of both mixed venous oxygen saturation and central venous oxygen saturation in a variety of clinical settings.

Although venous oxygen saturation has been subject of research for many years, increasing interest arose especially in the last decade for its use as a therapeutic goal in critically ill patients and during the perioperative period. Also, there has been debate on differences between mixed and central venous oxygen saturation and their interchangeability. Both mixed and central venous oxygen saturation are clinically useful but both variables should be used with insightful knowledge and caution. In general, low values warn the clinician about cardiocirculatory or metabolic impairment and should urge for further diagnostics and appropriate action, whereas normal or high values do not rule out persistent tissue hypoxia. The use of venous oxygen saturations seems especially useful in the early phase of disease or injury. Whether venous oxygen saturations should be measured continuously remains unclear. Especially continuous measurement of central venous oxygen saturation as part of treatment protocol has shown to be a valuable strategy in the emergency department and in cardiac surgery. In clinical practice venous oxygen saturations should always be used in combination with vital signs and other relevant endpoints.

Methods

We performed a search of the PUBMED database from 1980 to 2010 using combinations of the following terms: [SvO_2, $ScvO_2$, venous oxygen saturation, venous saturation, critically ill, shock, septic shock, high risk surgery, surgery, operation]. The articles published in English were included when published in a peer-reviewed journal. The clinical investigations had to concern adults. Additionally, bibliographies of relevant articles were screened as well.

Physiology

Understanding the physiology of venous saturations is essential for its effective application in critically ill patients and during the perioperative period.

SvO_2 depends on arterial oxygen saturation (SaO_2), the balance between oxygen demand (VO_2) and cardiac output (CO), and hemoglobin levels. According to the Fick principle [8], SvO_2 can be described by the following formula:

$$SvO_2 = \left[SaO_2 - VO_2 / CO\right] \left[1 / Hb \times 1{,}34\right]$$

Increased VO_2 will be compensated by increased CO. If this is not adequate, i.e. if O_2 demand is not met, elevated oxygen extraction in the peripheral tissues occurs and consequently SvO_2 will drop. Thus, SvO_2 reflects the balance between oxygen delivery and oxygen demand [9]. The normal range for SvO_2 is 65 to 75% [4,10]. Low SvO_2 is predictive of bad outcome [4,11], whereas normal or supra normal SvO_2 (or $ScvO_2$) values do not guarantee adequate tissue oxygenation [12,13]. If tissue is not capable of extracting oxygen, e.g. in case of shunting and cell death, venous return may have high oxygen content despite persistent cellular hypoxia.

A variety of physiological and pathological changes may influence venous saturation (figure 1) and thus require different therapeutic interventions. Recognition of the aetiology of any derangement is obligatory for the safe use of venous saturation as therapeutic goal.

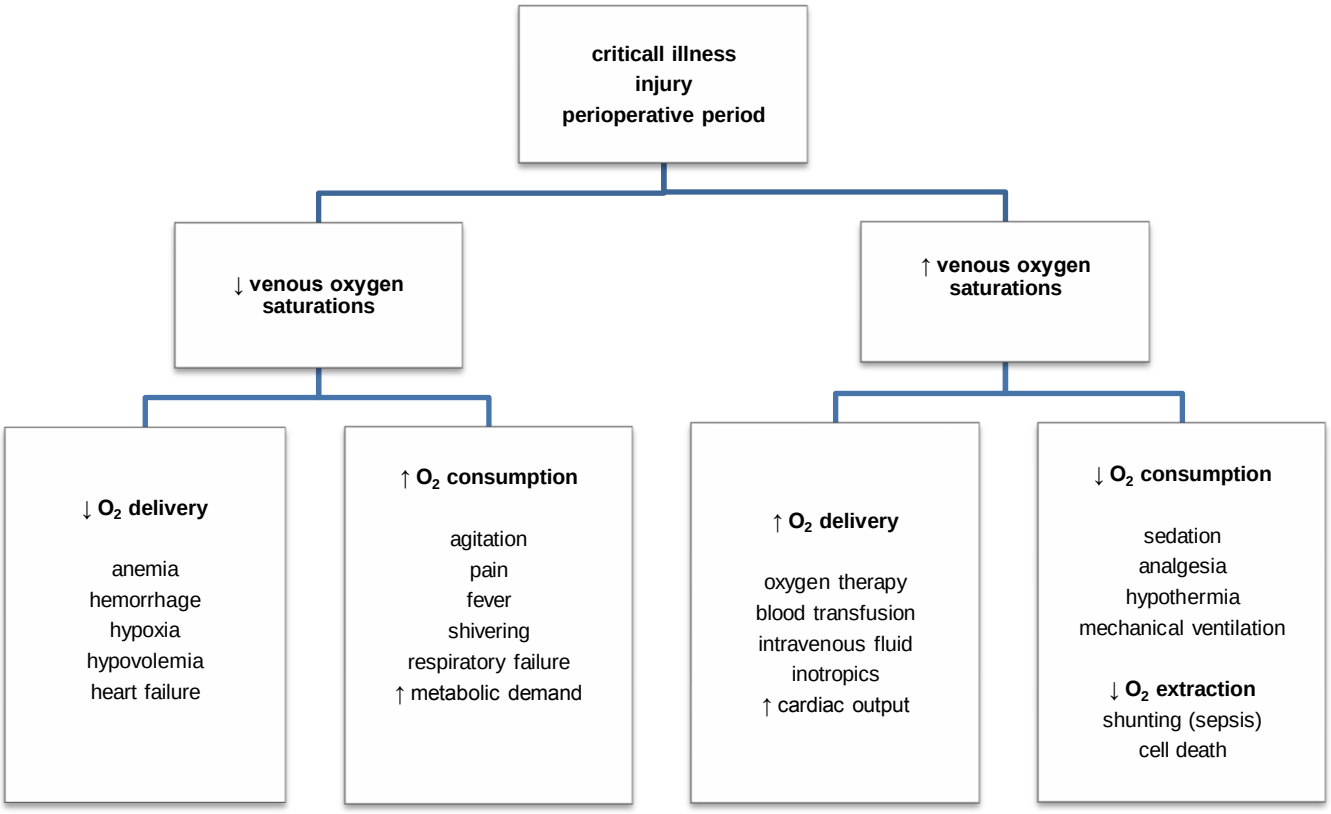

Figure 1. **Multiple physiologic, pathologic and therapeutic factors may influence the value of central venous oxygen saturation.**

Central versus mixed venous oxygen saturation (table 1)

In general there has been considerable debate on equality or interchangeability of $ScvO_2$ and SvO_2 [14-16]. In critically ill patients substituting SvO_2 by $ScvO_2$ results in large variability [16-21]. This could in part be explained by modifications of blood flow distribution

and oxygen extraction by brain and splanchnic tissue. In this situation, $ScvO_2$ may provide the false impression of adequate body perfusion. Also, whether a positive $ScvO_2$ – SvO_2 gradient can be used as a marker of greater O_2 utilization and predictor of survival remains subject of debate [20,22,23].

In contrast, others have stated that $ScvO_2$ could indeed be used as a substitute for SvO_2 [24-26]. For example, Reinhart et al. [24] performed continuous measurements of venous oxygen saturations in anesthetized dogs over a wide range of hemodynamic conditions, including hypoxia, haemorrhage and resuscitation, and described close tracking between $ScvO_2$ and SvO_2 [24]. However, correlation was lowest during hypoxia, one of the areas of greatest clinical interest. Nevertheless, precise determination of absolute values for SvO_2 from $ScvO_2$ was not possible, as was seen before [21,27-29].

Additionally, the relationship between cardiac output (CO) or cardiac index (CI) and venous saturations has been evaluated in critically ill patients. So far, for both SvO_2 and $ScvO_2$ the results were inconclusive. Larger trials are needed before clinical recommendations can be made regarding their clinical use [19,30-33].

Table 1. Studies comparing mixed venous oxygen saturation and central venous oxygen saturation

study	design and subjects	results	conclusions
Varpula et al [14]	n=16; septic shock; ICU 72 paired samples	mean SvO_2 below mean $ScvO_2$ at all time points; bias of difference 4.2%; 95% limits of agreement -8.1 to 16.5%; difference correlated with CI and DO_2	difference between $ScvO_2$ and SvO_2 varied highly; SvO_2 cannot be estimated on basis of $ScvO_2$
Martin et al [16]	n=7; 580 comparative measuremer critically ill patients; ICU with and without interventions	difference were equal or greater than 5% in 49% during periods of stability and in 50% during periods with interventions	$ScvO_2$ monitoring not reliable
Chawla et al [17]	n=32 postsurgical, n=21 medical; ICU	SvO_2 consistently lower than $ScvO_2$; mean (±SD) bias -5.2 ± 5.1%	SvO_2 and $ScvO_2$ not equivalent; substitution of $ScvO_2$ for SvO_2 in calculation of VO_2 resulted in unacceptably large errors
Kopterides et al [18]	n=37; septic shock	mean SvO_2 below mean $ScvO_2$; mean bias -8.5%; 95% limits of agreement -20.2 to 3.3%	$ScvO_2$ and SvO_2 not equivalent in septic shock; calculation of VO_2 resulted in unacceptably large errors
Ho et al [19]	n=20; cardiogenic or septic shock	$ScvO_2$ overestimated SvO_2 with mean bias 6.9%; 95% limits of agreement -5.0 to 18.8%; changes did not follow the line of perfect agreemen	$ScvO_2$ and SvO_2 are not interchangeable numerically
van Beest et al [20]	n=53; 265 paired samples; sepsis; ICU multi centre	mean SvO_2 below mean $ScvO_2$ at all time points; bias of difference 1.7% 95% limits of agreement -12.1 to 15.5%; identical results for change in $ScvO_2$ and SvO_2	$ScvO_2$ does not reliably predict SvO_2 in sepsis trend of $ScvO_2$ not superior in this context
Scheinmann et al [21]	n=24; critically ill cardiac patients; CCU	$ScvO_2$ > SvO_2 in shock changes in $ScvO_2$ reflect changes in SvO_2 (r=0.90) $ScvO_2$ from right atrium is similar to SvO_2 (r=0.96)	SvO_2 consistently lower than $ScvO_2$ poor correlation in heart failure or shock changes in $ScvO_2$ reflect changers in SvO_2
Dueck et al [25]	n=70; 502 comparative sets; neurosurgery	95% limits of agreement 6.8% to 9.3% for single va correlations between changes of SvO_2 and $ScvO_2$: r=0.755, p < 0.001	numerical $ScvO_2$ values not equivalent to SvO_2 in varying hemodynamic conditions; trend of $ScvO_2$ may be substituted for the trend of SvO_2
Reinhart et al [26]	n=32; critically ill patients; ICU continuous parallel measurements	$ScvO_2$ closely paralleled SvO_2; $ScvO_2$ averaged (±SD) 7±4% higher than SvO_2 $ScvO_2$ changed in parallel in 90% when SvO_2 chan	continuous fiberoptic measurement of $ScvO_2$ potentially reliable tool to rapidly warn of acute change in the oxygen supply / demand ratio
Ladakis et al [28]	n=31 surgical and n=30 medical; critically ill patients; ICU	significant difference between mean $ScvO_2$ and Sv r=0.945 for total population	$ScvO_2$ and SvO_2 are closely related and interchangeable for initial evaluation
Tahvanainen et al [29]	n=42; critically ill patients; ICU $ScvO_2$ as representative of real changes in pulmonary shunt	correlation between PA blood samples and both superior vena cava and right atrial blood samples	$ScvO_2$ can replace SvO_2; exact SvO_2 value can only be measured from PA

CCU, cardiac care unit; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; ICU, intensive care unit; VO_2, oxygen consumption; CI, cardiac index; DO_2, oxygen delivery; PA, pulmonary artery.

Clinical use of venous oxygen saturations (table 2)

Cardiac failure

Venous oxygen saturations have been shown to have diagnostic, prognostic, and therapeutic qualities in critically ill patients having an acute myocardial infarction. Mixed venous oxygen saturation was particularly reduced in patients with cardiogenic shock or left ventricular failure. Patients with cardiac failure are unable to increase cardiac output during periods of increased oxygen need. Changes in oxygen demand will therefore only be compensated by changes in oxygen extraction in the same direction and indicated by inverse changes in venous oxygen saturations. Consequently, a drop in venous oxygen saturations will be a marker of cardiac deterioration. Patients with low venous oxygen saturations in early disease stage may considered to be in shock [34,35]. Also, patients with sepsis and known decreased left ventricular function seem to benefit from early goal-directed therapy (EGDT) when treated for sepsis [36] according to the Surviving Sepsis Campaign guidelines [37]. Finally, in the setting of cardio pulmonary resuscitation (CPR) a $ScvO_2$ of 72% is highly predictive of return of spontaneous circulation [38].

Trauma

In the initial assessment of trauma patients an adequate judgement of possible blood loss is essential. Compared to conventional parameters venous oxygen saturations are superior in predicting blood loss [39,40]. Moreover, after major trauma with brain injury $ScvO_2$ values below 65% in the first 24 hours are associated with higher mortality (28-days mortality; 31.3% vs. 13.5%) and prolonged hospitalization (45 vs. 33 days) [41].

Table 2. Studies describing central venous oxygen saturation in clinical settings

study	design and subjects	results	conclusions
Rady et al [1]	n=36; critically ill patients; ED	additional therapy is needed after hemodynamic stabilization to normal blood pressure and heart rate	$ScvO_2$ and can be utilized to guide thearpy
Pope et al [13]	n=619 registries treated with EGDT observational study	groups: $ScvO_2$ < 70%, $ScvO_2$ 71-89%, $ScvO_2$ > 90% multivariate analysis: initial high $ScvO_2$ higher mortality	also high $ScvO_2$ values predictive for mortality
Ander et al [35]	controls n=17, high-lactate group n=22, low lactate group n=5; chronic congestive heart failure; ED	$ScvO_2$ lower in high lactate group than in low lactate group (32±12% vs. 51±13%) and control (60±6%); after treatment significant decrease of lactate and increase in $ScvO_2$ in the high lactate group compared to low lactate group	once patients with decompensated end-stage congestive heart failure are identified, aggressive alternative management is needed
Scalea et al [40]	n=26, trauma patients with suggested blood loss	despite stable vital signs 39% of the patients had $ScvO_2$ <65%; these patients required more transfusions; superiority $ScvO_2$ to predict blood loss	$ScvO_2$ reliable and sensitive method for detecting blood loss; it is a useful tool in the evaluation
Di Filippo et al [41]	n=121 brain injury after trauma; non-controlled study	nonsurvivors showed higher lactate, lower $ScvO_2$ values; patients with $ScvO_2$ ≤65% showed higher 28-day mortality, ICU LOS and hospital LOS than patients with $ScvO_2$ >65%	$ScvO_2$ <65% in first 24 hours in patients with major trauma is associated with prolonged LOS and higher mortality
Pearse et al [65]	n=118, major surgery	after multivariate analysis lowest CI and lowest $ScvO_2$ were associated with post-operative complications; optimal $ScvO_2$ cut-off for morbidity prediction:64.4%	oxygen consumption is also an important determinant of $ScvO_2$; reductions in $ScvO_2$ independently associated with post-operative complications
Rivers et al [73]	n=263; RCT; EGDT vs. controls severe sepsis, septic shock; ED	EGDT (goal: $ScvO_2$ ≥ 70%) showed better survival (absolute 16%), lower lactate; more fluids, red cell transfusion and inotropics	EGDT provides benefits to outcome
Trzeciak [74]	n=16 pre-EGDT n=22 EGDT	less PAC utilization; more fluids and dobutamine used; similar costs	EGDT endpoint can reliably be achieved
Kortgen [75]	n=30 controls; n=30 septic shock implementation procedure septic shock	use of dobutamine, insulin, hydrocortisone and aPC increased; amount of fluids and packed bloods cells unaffected; mortality in lower after implementation	implementation of sepsis bundle feasible survival benefit
Jones [76]	n=79 pre-intervention n=77 post-intervention ED	controls: more renal failure at baseline greater crystalloid volume and vasopressor infusion mortality 18 vs. 27%	mortality reduction
Micek [78]	n=60 before implementation n=60 after implementation ED	more appropriate antimicrobial regimen more fluids, more vasopressors less vasopressor by time of transfer to ICU	shorter hospital LOS lower 28-day mortality
Shapiro [80]	n=51 historical controls n=79 septic shock	patients received more fluids, earlier antibiotics, more vasopressors, tighter glucose control; not more packed blood cells	implementation sepsis protocol feasible no survival benefit
Jones et al [94]	multicentre, randomized; n=300 severe sepsis, septic shock goals: lactate clearance vs. $ScvO_2$	higher in hospital mortality $ScvO_2$; no significant difference (predefined -10% threshold)	no significant different mortality between normalization of lactate clearance compared to normalization $ScvO_2$

ED, emergency department; $ScvO_2$, central venous oxygen saturation; EDGT, early goal-directed therapy; RCT, randomized controlled trial; ICU LOS, length of stay in intensive care unit; hospital LOS, length of stay in hospital; CI, cardiac index; SAPS II, simplified acute physiology score; ICU, intensive care unit.

High-risk surgery

In cardiac surgery patients, SvO_2 has been shown to be superior to mean arterial pressure (MAP) and heart rate as qualitative warning sign of substantial hemodynamic deterioration. However, results on predictive value of SvO_2 for CO in clinical settings are inconsistent [42-44]. Nevertheless, continuous SvO_2 monitoring enables the early diagnosis of occult bleeding or could show poor tolerance of a moderate anaemia due to the inability of the patient with chronic heart dysfunction or preoperative negative inotropic treatment (e.g. beta-blockers) to increase CO in the face of anaemia. Furthermore, temporary decreases of SvO_2 values after cardiac surgery are of prognostic value and may predict the development of arrhythmias [45-47]. Also, probably due to increased oxygen extraction ratio (O_2ER) decreased SvO_2 values during weaning from mechanical ventilation are predictive for extubation failure [48-50]. Finally, good predictive values of SvO_2 for mortality have been described [51,52]. This suggests beneficial effects of SvO_2 monitoring, at least during and after cardiac surgery.

Goal Directed Therapy (GDT) has been shown to improve outcome after major general surgery [53] Originally, the goals in the protocol group were supra-normal hemodynamic and oxygen transport values (CI > 4.5 L/min/m^2, DO_2 > 600 ml/min/m^2, VO_2 > 170 ml/min/m^2). In this group a significant reduction of complications, hospital stay, duration of mechanical ventilation and mortality was achieved when the PAC was placed preoperatively [54]. However, such strict predefined concept holds certain risks and should not be translated to all patients [55-57]. Meta-analyses of hemodynamic optimization in high risk patients revealed hemodynamic optimization to be beneficial only when interventions were commenced before development of organ failure [58,59]. Several of the studies described showed improved outcome, possibly including long-term survival, when GDT was commenced before surgery [54,60-62]. Maybe due to methodological shortcomings, a multi-centre trial that randomised surgical patients to PAC guided or conventional management failed to show a difference in outcome [63,64]. More recently a reduction in post-operative

complications and duration of hospital stay was described when GDT was used post-operatively [65-67]. However, the abovementioned findings do not provide definite answers on how to use venous saturations as a therapeutic goal. Only one interventional trial used $ScvO_2$ as a therapeutic goal in perioperative care [68]. After achieving predefined goals for arterial pressure, urine output, and central venous pressure, the intervention group received therapy to achieve the additional goal of an estimated oxygen extraction ratio < 27%. Fewer patients developed organ failure in the $ScvO_2$ group [68].

Sepsis and septic shock

In a large multi-centre study 3 different cohorts of a very heterogeneous population of critically ill patients were compared for survival after different strategies for hemodynamic therapy had been applied: control vs. supra-normal values for the cardiac index (> 4.5L/min/m^2) or normal values for mixed venous saturation. In total, the anticipated goal was only achieved in one third of the patients. There was no significant reduction in morbidity or mortality in any group [69]. An important reason for this may be the late timing of the intervention, i.e. after occurrence of organ failure, implying that all patients suffered severe damage and received significant treatment before inclusion.

Global tissue hypoxia as a result from systemic inflammatory response or circulatory failure is an important indicator of shock preceding multiple organ dysfunction syndrome (MODS). The development of MODS predicts outcome of the septic patient [37]. Treatment strategies aimed at restoring the balance between DO_2 and VO_2 by maximizing DO_2 have not been successful [57,69,70].

In line with studies over several decades [1,21,27,35,40,71] and based on recommendations [72] Rivers *et al.* randomized 263 patients with severe sepsis or septic shock to standard therapy or EGDT. Compared with the conventionally treated group, the $ScvO_2$ guided group received more fluids, more frequently dobutamine, and more blood

transfusion during the first 6 hours. This resulted in an absolute reduction in 28-day mortality of 16% [73].

A large amount of studies that implemented certain treatment protocols at the emergency department, including antibiotic therapy and tight glucose control for example, [74-79] showed significant decrease in mortality. EGDT endpoints (CVP 8-12 mmHg, MAP ≥ 65 mmHg, and $ScvO_2$ ≥ 70%) can well be achieved in an ED setting suggesting that a multifactor approach is a useful strategy in the treatment of sepsis [74-80]. Of note, three of these studies described similar populations with high percentage end-stage renal disease in the control group being prone for higher mortality [76,77,79,81]. Although attainment of an $ScvO_2$ >70% has been reported as prominent factor for survival [82] several studies in which EGDT without that specific target was used were able to achieve a survival benefit as well [83-85]. In summary, as shown by Nguyen *et al* [86], the use of (modified) EGDT implies early recognition of the critically ill patient and enforces continuous reassessment of treatment. This seems to be the greatest gain in the treatment of patients with severe sepsis or septic shock over the last decade.

Earlier studies that enrolled patients admitted at the intensive care unit (ICU) were unable to show a decrease in mortality after aggressive hemodynamic optimization [57,69]. In contrast, more recent studies that used modified EGDT protocols were able to show an significant decrease in mortality [85,87,88], suggesting that compliance to dedicated sepsis bundles after the ED stage can still be useful.

However, low incidences of low $ScvO_2$ values at ICU admission [89] or emergency department (ED) presentation [90] do occur together with baseline mortality compared to the original EGDT study [73,89,90]. For clinical appreciation of the abovementioned results a thorough look into the data is needed. Interestingly, in the EGDT study [73] less patients were intubated before first $ScvO_2$ sampling and this could partially explain the difference of initial $ScvO_2$ values between both studies [73,89]: due to higher DO_2 (pre-oxygenation) and

lower VO_2 (sedation, paralysis; lower work of breathing) $ScvO_2$ may very well improve in response to emergency intubation in the majority of patients [91]. This partially explaines the differences between populations [73,89,90] and provides another piece in the puzzle on the value of $ScvO_2$ [93]. Nevertheless, applicability of the results of the EGDT trial may be dependent on geographical setting and underlying health care system [92,93].

Additionally, no difference in outcome was found between a resuscitation protocol based on lactate clearance and a $ScvO_2$ based protocol [94] and $ScvO_2$ optimization does not always exclude a decrease in lactate levels [95]. Also, the pursuit of $ScvO_2$ values >70% does not always seem to be the optimal solution. Recent data suggest that also patients with initially high $ScvO_2$ values may have adverse outcomes [12,13], probably due to impaired oxygen utilization. High $ScvO_2$ values may thus represent an inability of the cells to extract oxygen or microcirculatory shunting in sepsis [96].

Finally, as a reflection of increased respiratory muscles O_2ER a reduced $ScvO_2$ or SvO_2 predicts extubation failure in difficult-to-wean patients [48,97]. However, a successful intervention to increase $ScvO_2$ in this context is not known yet. Nevertheless, it is conceivable that in the future $ScvO_2$ will be used as a parameter in weaning protocols for a subset of patients [97,98].

Continuous measurement

Should continuous measurement be considered when venous saturations are used as a therapeutic goal? It may be argued that changes in venous saturations may occur rapidly, particularly in hemodynamically instable patients, and that discontinuous spot measurements by drawing intermittent blood samples may miss these changes. Accordingly, continuous measurement of SvO_2 in septic shock patients revealed a higher frequency of short-term changes in SvO_2 in nonsurvivors. Thus, variations in SvO_2 could be of prognostic

importance [99]. However, lack of therapeutic guidelines and cost effectiveness issues [5,7,58] question the clinical use of continuous measurement of SvO_2 in critically ill. Continuous measurement in perioperative care allows detection of fluctuations. Low SvO_2 values have been associated with increased complications and morbidity, especially in cardiac surgery [100] and myocardial infarction and use of a SvO_2>70% as a target seemed promising [38,43].

There are currently two commercially available devices to measure $ScvO_2$ continuously. Continuous $ScvO_2$ measurement as part of treatment protocol has shown to be a valuable strategy in the ED [71,73] and in cardiac surgery [101]. Additionally, Reinhart et al. concluded that continuous $ScvO_2$ measurement in the ICU setting is potentially reliable [26]. However, continuous and intermittent measurements of SvO_2 or $ScvO_2$ have never been compared systematically.

Conclusions

The on-going debate on differences between SvO_2 and $ScvO_2$ and their interchangeability should focus on well defined populations. Both SvO_2 and $ScvO_2$ are clinically useful but both variables should be used with knowledge and caution. Evaluating the available evidence in a clinical setting, we conclude that low venous oxygen saturations are an important warning sign of the inadequacy of systemic oxygen delivery to meet oxygen demands. Low values may warn the clinician about cardiocirculatory or metabolic impairment and should urge for further diagnostics and appropriate action, whereas normal or high values do not rule out persistent tissue hypoxia. Based on the numerous clues for its usefulness referred in this article the use of venous oxygen saturations seems especially useful in the early phase of disease or injury. In clinical practice venous oxygen saturations should always be used in combination with vital signs and other relevant endpoints.

References

1. Rady MY, Rivers EP, Novak RM: **Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate.** *Am J Emerg Med* 1996, **14**:218-225.
2. Wo CC, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E: **Unreliability of bloodpressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness.** *Critical Care Medicine* 1993, **21**: 218-223.
3. Vincent JL, De Backer D: **Oxygen uptake/oxygen supply dependency: fact or fiction?** *Acta Anaesthesiol Scand Suppl* 1995, **107**:229-237.
4. Kandel G, Aberman: **A Mixed venous oxygen saturation: its role in the assessment of the critically ill patient.** *Arch Int Med* 1983, **143**: 1400-1402.
5. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell Jr FE, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson Jr WJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA: **The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT investigators**. *JAMA* 1996, **276**: 889-897.
6. Sakr Y, Vincent JL, Reinhart K, Payen D, Wiedermann CJ, Zandstra DF, Sprung CL: **Use of the pulmonary catheter is not associated with worse outcome in the ICU**. *Chest* 2005, **128**: 2722-2731.
7. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, Rowan K: **Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial.** *Lancet* 2005, **366**: 472-477.
8. Fick A: **Ueber die Messung des Blutquantums in den Herzventrikeln**. *Verhandl Physik Med Gesellschafft Wurzburg* 1870, **2**: 16-28.
9. Reinhart K: **Monitoring O_2 transport and tissue oxygenation in critically ill patients.** In: Reinhart K, Eyrich K (ed) Clinical aspects of O_2 transport and tissue oxygenation. Springer Berlin Heidelberg New York pp 195-211**.**
10. Nelson LD: **Continuous venous oximetry in surgical patients**. *Ann Surg* 1986, **203**: 329-333.

11. Kasnitz P, Druger Gl, Yorra F, Simmons DH: **Mixed venous oxygen tension and hyperlactataemia. Survival in severe cardiopulmonary disease**. *JAMA* 1976, **236**: 570-574.

12. Perz S, Uhlig T, Kohl M, Bredle DL, Reinhart K, Bauer M, Kortgen A: **Low and „supranormal" central venous oxygen saturation and markers of tissue hypoxia in cardiac surgery patients: a prospective observational study**. *Intensive Care Med* 2011, **37**: 52-59.

13. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI (EMShockNet): **Multicenter study of central venous oxygen saturation ($ScvO_2$) as a predictor of mortality in patients with sepsis**. *Ann Emerg Med* 2009, **55**: 40-46.

14. Varpula M, Karlsson S, Ruokonen E, Pettilä V: **Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock**. *Intensive Care Med* 2006, **32**:1336-1343

15. Edwards JD, Mayall RM: **Importance of the sampling site for measurement of mixed venous oxygen saturation in shock**. *Crit Care Med* 1998, **26**: 1356-1360.

16. Martin C, Auffrey J, Badetti C, Perrin G, Papazian L, Gouin F: **Monitoring of central venous oxygen saturation versus mixed oxygen saturation in critically ill patients.** *Intensive Care Med* 1992, **18**: 101-104.

17. Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M: **Lack of equivalance between central and mixed venous oxygen saturation**. *Chest* 2004, **126**: 1891-1896.

18. Kopterides P, Bonovas S, Mavrou I, Kostadima E, Zakynthinos E, Armaganidis A: **Venous oxygen saturation and lactate gradient from superior vena cava to pulmonary artery in patients with septic shock**. *Shock* 2008; **31**: 561-567.

19. Ho KM, Harding R, Chamberlain J, Bulsara: **A comparison of central and mixed venous oxygen saturation in circulatory failure.** *J Cardiothorac Vasc Anesth* 2010, **24**: 434-439.

20. van Beest PA, van Ingen J, Boerma EC, Holamn ND, Groen H, Koopmans M, Spronk PE, Kuiper MA: **No agreement of mixed venous and central venous saturation in sepsis, independent of sepsis origin**. *Crit Care* 2010, **14**: R219.

21. Scheinman MM, Brown MA, Rapaport E: **Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients**. Circulation 1969, **40**: 165-172.

22. Sander M, Spies CD, Foer A, Weymann L, Braun J, Volk T, Grubitzsch H, von Heymann C: **Agreement of central venous saturation and mixed venous saturation in cardiac surgery paients.** *Intensive Care Med* 2007, **33**:1719-1725.

23. Gutierrez G, Comignanni P, Huespe L, Hurtado FJ, Dubin A, Jha V, Arzani Y, Lazzeri S, Sosa L, Riva J, Kohn W, Suarez D, Lacuesta G, Olmos D, Mizdraji C, Ojeda A: **Central venous to mixed venous blood oxygen and lactate gradients are associated with outcome in critically ill patients.** *Intensive Care Med* 2008, **34**:1662-1668.

24. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM: **Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand.** *Chest* 1989, **95**: 1216-1221.

25. Dueck MH, Klimek M, Appenrodt S, Weigand C, Boerner U: **Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions**. *Anesthesiology* 2005, **103**: 249-257.

26. Reinhart K, Kuhn HJ, Hartog C, Bredle DL**: Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill**. *Intensive Care Med* 2004, **30**: 1572-1578.

27. Lee J, Wright F, Barber R, Stanley L: **Central venous oxygen saturation in shock: a study in man**. *Anesthesiology* 1972, **36**: 472-478.

28. Ladakis C, Myrianthefs P, Karabinis A, Karatzas G, Dosios T, Fildissis G, Gogas J, Baltopoulos G: **Central venous and mixed venous oxygen saturation in critically ill patients**. *Respiration* 2001, **68**: 279-285.

29. Tahvanainen J, Meretoja O, Nikki P: **Can central venous blood replace mixed venous blood samples?** *Crit Care Med* 1982, **10**: 758-761.

30. Vaughn S, Puri VK: **Cardiac output changes and continuous mixed venous oxygen saturation measurement in the critically ill**. *Crit Care Med* 1988, **16**: 495-498.

31. Ruokonen E, Takala J, Uusaro A: **Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation**. *Crit Care Med* 1991, **19**: 1365-1369.

32. Mahutte CK, Jaffe MB, Sasse SA, Chen PA, Berry RB, Sassoon CS: **Relationship of thermodilution cardiac output to metabolic measurements and mixed venous oxygen saturation**. *Chest* 1993, **104**: 1236-1242.

33. Perner A, Haase N, Wiis J, White JO, Delany A: **Central venous oxygen saturation for the diagnosis of low cardiac output in septic shock patients**. *Acta Anaesthesiol Scand* 2010, **54**: 98-102.

34. Kan K, Koeda T, Ichikawa T, Suzuki T, Kaeakami M, Miura S, Nasu M, Ishikawa M, Koh E, Sato M, Suzuki T, Kato M: **Relation between mixed venous blood oxygen saturation and cardiac pumping function at the acute phase of myocardial infarction**. *Jap Circ J* 1989, **53**: 1481-1490.

35. Ander DS, Jaggi M, Rivers E, Rady MY, Levine TB, Levine AB, Masura J, Gryzbowski M: **Undected cardiogenic shock in patients with congestive heart failure presenting to the emergency department.** *Am J Cardiol* 1998, **82**: 888-891.

36. Shah S, Ouellette DR: **Early goal-directed therapy for sepsis in patients with preexisting left ventricular dysfunction: a retrospective comparison of outcomes based upon protocol adherence**. *Chest* 2010, **138**: 897A.

37. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock**. *Crit Care Med* 2008, **34**: 17-60.

38. Rivers EP, Martin GB, Smithline, Rady MY, Schultz CH, Goetting MG, Appleton TJ, Nowak RM: **The clinical implications of continuous central venous oxygen saturation during human CPR**. *Ann Emerg Med* 1992, **21**: 1094-1101.

39. Scalea T, Holman M, Fuortes M, Baron BJ, Phillips TF, Goldstein AS, Sclafani SJA, Shaftan GW: **Central venous blood oxygen saturation: an early, accurate measurement of volume during hemorrhage**. *J Trauma* 1988, **28**: 725-732.

40. Scalea TM, Hartnett RW, Duncan AO, Atweh NA, Phillips TF, Sclafani SJA, Fuortes M, Shaftan GW: **Central venous oxygen saturation: a useful clinical tool in trauma patients**. *J Trauma* 1990, **30**: 1539-1543.

41. Di Filippo A, GonnelliC, Perretta L, Zagli G, Spina R, Chiostri M, Gensini GF, Peris A: **Low central venous saturation predicts poor outcome in patients with brain injury after major trauma: a prospective observational study**. *Scand J Trauma, Resusc Emerg Med* 2009, **17**: 17-23.

42. Waller JL, Kaplan JA, Bauman DI, Craver JM: **Clinical evaluation of a new fiberoptic catheter oximeter during cardiac surgery.** *Anesth Analg* 1982, **61**: 676-679.

43. Magilligan DJ, Teasdall R, Eisinminger R, Peterson E: **Mixed venous oxygen saturation as a predictor of cardiac output in the postoperative cardiac surgical patient.** *Ann Thor Surg* 1987, **44**: 260-262.

44. Kirkeby-Garstad I, Sellevold OFM, Stenseth R, Skogvoll E, Karevold A: **Post-operative myocardial dysfunction does not affect the physiological response to early mobilization after coronary artery bypass grafting.** *Acta Anaesthiol Scand* 2004, **49**: 1241-1247.

45. Trouwborst A, Tenbrinck R, Van Woerkens EC: **Bloodgas analysis of mixed venous blood during normoxic acute isovolemic hemodilution in pigs**. *Anesth Analg* 1990, **70**: 523-529.

46. De la Rocha AG, Edmonds JF, Williams WG, Poirier C, Trusler RN: **Importance of mixed venous oxygen saturation in the care of critically ill patients.** *Can J Surg* 1978, **21**: 227-229.

47. Hines R, Rafferty T: **Right ventricular ejection fraction catheter: toy or tool?** *J Cardiothor Vasc Anesth* 1993, **7**: 236-240.

48. Jubran A, Mathru M, Dries D, Tobin MJ: **Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof**. *Am J Respir Crit Care Med* 1998, **158**: 1763-1769.

49. Cason CL, DeSalvo SK, Ray WT: **Changes in oxygen saturation during weaning from short-term ventilator support after coronary bypass graft surgery**. *Heart Lung* 1994, 23: 368-375.

50. Armaganidis A, Dhainaut JF: **Weaning from artificial respiration: values of continuous monitoring of mixed venous oxygen saturation**. *Ann Fr Anesth Reanim* 1989, **8**: 708-715.

51. Polonen P, Ruokonen E, Hippelainen M, Pöyhönen M, Takala J: **A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients**. *Anesth Analg* 2000, **90**: 1052-1059.

52. Holm J, Håkanson RE, Vánky F, Svedjeholm R: **Mixed venous oxygen saturation is a prognostic marker after surgery for aortic stenosis**. *Acta Aneasthesiol Scand* 2010, **54**: 589-595.

53. Hamilton MA, Cecconi M, Rhodes A: **A systemic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients**. *Anesth Analg* 2010, DOI: 10.1213/ANE.0b013e3181eeaae5.

54. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee T-S: **Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients**. *Chest* 1988, **94**: 1176-1186.

55. McKinley BA, Kozar RA, Cocanour CS, Valdivia A, Sailors RM, Ware DN, Moore FA: **Normal versus supranormal oxygen delivery goals in shock resuscitation: the response is the same**. *J Trauma* 2002, **53**: 825-832.

56. Velmahos GC, Demetriades D, Shoemaker WC, Chan LS, Tatevossian R, Wo CC, Vassiliu P, Cornwel EE 3rd, Murray JA, Roth B, Belzberg H, Asensio JA, Berne TV: **Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial**. *Ann Surg* 2000, **232**: 409-418.

57. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D: **Elevation of systemic oxygen delivery in the treatment of critically ill patients**. *New Engl J Med* 1994, **330**: 1717-1722.

58. Kern JW, Shoemaker WC: **Meta-analysis of hemodynamic optimization in high-risk patients**. *Crit Care Med* 2002, **30**: 1686-1692.

59. Jones AE, Brown MD, Trzeciak S, Shapiro NI, Garret JS, Heffner AC, Kline JA: **The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis**. *Crit Care Med* 2008, **36**: 2734-2739.

60. Boyd O, Grounds RM, Bennet ED: **A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients**. *JAMA* 1993, **270**: 2699-2707.

61. Rhodes A, Cecconi M, Hamilton M, Poloniecki J, Woods J, Boyd O, Bennett D, Grounds RM: **Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study.** *Intensive Care Med* 2010, **36**: 1327-1332.

62. Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E: **Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery**. *Br Med J* 1999, **318**: 1099-1103.

63. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, Jacka M: **A randomized, controlled trial of the use of pulmonray-artery catheters in high-risk surgical patients**. *New Engl J Med* 2003, **348**: 5-14.

64. De Backer D, Creteur J, Vincent JL: **Perioperative optimization and right heart catheterization: what technique in which patient?** *Crit Care* 2003, **7**: 201-202.

65. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED: **Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised controlled trial [ISRCTN38797455]** *Crit Care* 2005, **9**: R687-R693.

66. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED: **Changes in central venous saturation after major surgery, and association with outcome**. *Crit Care* 2005, **9**: R694.

67. Collaborative Study Group on Perioperative $ScvO_2$ Monitoring: **Multicentre study on peri- and postoperative central venous oxygen saturation in high-risk surgical patients**. *Crit Care* 2006, **10**: R158.

68. Donati A, Loggi S, Preiser JC, Orsetti G, Münch C, Gabbanelli V, Pelaia P, Pietropaoli P: **Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients.** *Chest* 2007, **132**: 1817-1824.

69. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R: **A trial of goal-oriented hemodynamic therapy in critically ill patients**. *New Engl J Med* 1995, **333**: 1025-1032.

70. Alía I, Esteban A, Gordo F, Lorente JA, Diaz C, Rodriguez JA, Frutos F: **A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock**. *Chest* 1999, **115**: 453-461.

71. Rady MY, Rivers EP, Martin GB, Smithline H, Appelton T, Nowak RM: **Continuous central venous oximetry and shock index in the emergency department: use in the evaluation of clinical shock**. *Am J Emerg Med* 1992, **10**: 538-541.

72. Task force of the American College of Critical Care Medicine, Society of Critical Care Medicine: **Practice parameters for hemodynamic support in adult patients in sepsis**. *Crit Care Med* 1999, **27**: 639-660.

73. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; for the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**: 1368-1377.

74. Trzeciak S, Dellinger RP, Abate NL, Cowan RM, Stauss M, Kilgannon JH, Zanotti S, Parrillo JE: **A 1-year experience with implementing Early Goal-Directed Therapy for septic shock in the emergency department**. *Chest* 2006, **129**: 225-232.

75. Kortgen A, Niederprüm, Bauer M: **Implementation of an evidence-based "standard operating procedure"and outcome in septic shock**. *Crit Care Med* 2006, **34**: 943-949.

76. Jones AE, Focht A, Horton JM, Kline JA: **Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock**. *Chest* 2007, **132**: 425-432.

77. Puskarich MA, Marchick MR, Kline JA, Steuerwald MT, Jones AE: **One year mortality of patients treated with an emergency department based early goal directed therapy protocol for severe sepsis and septic shock: a before and after study**. *Crit Care* 2009, **13**: R167.

78. Micek ST, Roubinian N, Heuring T, Bode M, Williams J, Harrison C, Murphy T, Prentice D, Ruoff BE, Kollef MH: **Before-after study of a standardized hospital order set for the management of septic shock**. *Crit Care Med* 2006, **34**: 2707-2713.

79. Focht A, Jones AE, Lowe TJ: **Ealry goal-directed therapy: improving mortality and morbidity of sepsis in the emergency department**. *Jt Comm J Qual Patient Saf* 2009, **35**: 186-191.

80. Shapiro NI, Howell MD, Talmor D, Lahey D, Ngo L, Buras J, Wolfe RE, Weiss JW, Lisbon A: **Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol.** *Crit Care Med* 2006, **34**: 1025-1032.

81. Sarnak MJ, Jaber BL: **Mortality caused by sepsis in patients with end-stage renal disease compared with the general population**. *Kidney Int* 2000, **58**: 1758-1764.

82. Castellanos-Ortega A, Suberviola B, Garcia-Astudillo LA, Holanda MS, Ortiz F, Llorca J, Delgado-Rodriguez M: **Impact of the Surviving Spesis Campaign protocols on hospital length of stay and mortality in septic shock patients: results of a three-year follow-up quasi-expirimental study**. Crit Care Med 2010, 38: 1036-1043.

83. Gao F, Melody T, Daniels DF, Giles S, Fox S: **The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study**. *Crit Care* 2005, **9**: R764-R770.

84. Sebat F, Johnson D, Musthafa AA, Watnik M, Moore S, Henry K, Saari M: **A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients**. *Chest* 2005, **127**: 1729-1743.

85. Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP: **A modified goal-directed protocol improves clinical outcome in intensive care unit patients with septic shock: a randomized controlled trial**. *Shock* 2006, **26**: 551-557.

86. Nguyen HB, Corbett SW, Steele R, Banta J, Clark RT, Hayes SR, Edwards J, Cho TW, Wittlake WA: **Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality**. *Crit Care Med* 2007; **35**: 1105-1112.

87. Moore LJ, Jones SL, Kreiner LA, McKinley B, Sucher JF, Todd SR, Turner KL, Valdivia A, Moore FA: **Validation of a screening tool for early identification of sepsis**. *J Trauma* 2009, **66**: 1539-1547.

88. Zambon M, Ceola M, Almeida-de-Castro R, Gullo A, Vincent JL: **Implementation of the Surviving Sepsis Campaign guidelines for severe sepsis and septic shock: we could go faster**. *J Crit Care* 2008, **23**: 455-460.

89. van Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk PE, Kuiper MA: **The incidence of low venous oxygen saturation on admission in the ICU: a multicenter observational study in the Netherlands**. *Crit Care* 2008; **12**: R33.

90. Ho BCH, Bellomo R, McGain F, Jones D, Naka T, Wan L, Braitberg G: **The incidence and outcome of septic shock patients in the absence of early-goal directed therapy.** *Crit Care* 2006; **10**: R80.

91. Hernandez G, Peña H, Cornejo R, Rovegno M, Retamal J, Navarro JL, Aranguiz I, Castro R, Bruhn A: **Impact of emergency intubation on central venous oxygen saturation in critically ill patients: a multicenter observational study**. *Crit Care* 2009, **13**: R63.

92. Bellomo R, Reade MC, Warrillow SJ: **The pursuit of high central venous oxygen saturation in sepsis: growing concerns.** *Crit Care* 2008, **12**: 130.

93. Stahl W, Radermacher P, Georgieff M, Bracht H: **Central venous oxygen saturation and emergency intubation – another piece in the puzzle?** *Crit Care* 2009, **13**: 172.

94. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA (EMShockNet): **Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy.** *JAMA* 2010, **303**:739-746.

95. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, Parrillo JE, Dellinger RP, Trzeciak S (EMShockNet): **Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis**. *Shock* 2009, **32**: 35-39.

96. Ince C, Sinaasappel M: **Microcirculatory oxygenation and shunting in sepsis and shock**. *Crit Care Med* 1999, **27**: 1369-1377.

97. Teixeira C, Brandao da Silva N, Savi A, Rios Veiira SR, Nasi LA, Friedman G, Pinheiro Oliveira R, Viegas CremoneseR, Tonietto TF, Bressel MAB, Maccari JG, Wickert R, Borges LG: **Central venous saturation is a predictor of reintubation in difficult-to-wean patients**. *Crit Care Me*d 2010, **38**: 491-496.

98. Wratney AT: **Central venous saturation as a predictor of extubation failure**. *Crit Care Med* 2010, **38**: 708-709.

99. Krafft P, Steltzer H, Hiesmayr: **Mixed venous oxygen saturation in critically ill septic shock patients: The role of defined events. Chest** 1993, **103**: 900-906.

100. Pond CG, Blessios G, Bowlin J, McCawley C, Lappas DG: **Perioperative evaluation of a new mixed venous oxygen saturation catheter in cardiac surgery patients**. *J Cardiothorac Vasc Anesth* 1992, **6**: 280-282.

101. Smetkin AA, Kirov MY, Kuzkov VV,Lenkin AI, Eremev AV, Slastilin VY, Borodin VV, Bjertnaes LJ: **Single transpulmonary thermodilution and continuous monitoring of central venous oxygen saturation during off-pump coronary surgery.** *Acta Anaesthesiol Scand* 2009, **53**: 505-514.

Chapter 2

The incidence of low venous oxygen saturation on admission in the ICU: a multicenter observational study in the Netherlands

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Abstract

Introduction Low mixed or central venous saturation ($S(c)vO_2$) can reveal global tissue hypoxia and therefore can predict poor prognosis in critically ill patients. Early goal directed therapy (EGDT), aiming at a $ScvO_2 \geq 70\%$, has been shown to be a valuable strategy in patients with sepsis or septic shock and is incorporated in the Surviving Sepsis Campaign guidelines.

Methods We determined central venous pressure (CVP), hematocrit, pH, lactate and $ScvO_2$ or SvO_2 in a heterogeneous group of critically ill patients early after admission to the intensive care units (ICUs) in 3 Dutch hospitals.

Study design Prospective observational multicenter study.

Results Data of 340 acutely admitted critically ill patients were collected. The mean SvO_2-value was > 65% and the mean $ScvO_2$ was >70%. With mean CVP of 10.3 ± 5.5 mmHg, lactate plasma levels of 3.6 ± 3.6 and APACHE II-scores of 21.5 ± 8.3, the in-hospital mortality of the total heterogeneous population was 32.0%. A subgroup of septic patients (n = 125) showed a CVP of 9.8 ± 5.4 mmHg, mean $ScvO_2$ values of 74.0 ± 10.2% - where only 1% in this subgroup revealed a $ScvO_2$-value < 50% - and lactate plasma levels of 2.7 ± 2.2 mmol/L with APACHE II-scores 20.9 ± 7.3. Hospital mortality of this subgroup was 26%.

Conclusion The incidence of low $ScvO_2$ values on acutely admitted critically ill patients is low in Dutch ICUs. This is especially true for patients with sepsis / septic shock.

Introduction

Global tissue hypoxia as a result from systemic inflammatory response or circulatory failure is an important indicator of shock preceding multiple organ dysfunction syndrome (MODS). The development of MODS predicts outcome of the septic patient [1]. Unrecognized and untreated global tissue hypoxia increases morbidity and mortality. Accurate detection of global tissue hypoxia is therefore of vital importance. Physical findings, vital signs, measuring central venous pressure (CVP) and urinary output are of the utmost importance, but not always sufficient for accurate detection of global tissue hypoxia [2,3].

It is now generally accepted that a decreased central venous saturation ($ScvO_2$) obtained from a central venous catheter, can reveal a mismatch between oxygen supply and oxygen demand, hence global tissue hypoxia [1]. Decreased values predict poor prognosis after cardiovascular surgery [4], in severe cardiopulmonary disease [5], and in septic or cardiogenic shock [6,7]. $ScvO_2$ and SvO_2 (mixed venous oxygen saturation) therefore can be used as hemodynamic goals during resuscitation. According to Rivers *et al*. [8] hemodynamic optimization demands 'early goal-directed therapy' (EGDT), including $ScvO_2$-guided treatment. It was concluded that goal-oriented manipulation of cardiac preload, afterload and contractility, to achieve a balance between systemic oxygen delivery and oxygen demand is a valuable strategy in patients with sepsis or septic shock during the resuscitation period in the emergency department (ED) [8]. More recently, as a result of this study, an EGDT treatment protocol was included in the 'Surviving Sepsis Campaign' guidelines [1]. Also, several studies on implementation of such a protocol, partially in combination with other recommendations, have been published over the last years [9-11].

Based on clinical experience it seemed that the syndrome targeted in the EGDT study [8], was not very common in our ICUs and thus EGDT not being commonly indicated. Main purpose of this study was to determine the incidence of low $ScvO_2$ values in our geographical setting. We monitored a heterogeneous group of critically ill patients during unplanned

admission in 3 Dutch multidisciplinary ICUs. Also, *illustratively*, we compared the subgroup of septic patients with the population of septic patients as described by Rivers *et al* [8], with respect to $ScvO_2$ and other base-line characteristics.

Methods

Study centers

We studied ICU populations in one academic ICU [Academic Medical Center (AMC) in Amsterdam, The Netherlands] and two nonacademic ICUs [Gelre Hospital (GH) location Lukas in Apeldoorn, The Netherlands; Medical Center Leeuwarden (MCL) in Leeuwarden, The Netherlands]. The AMC is a large teaching hospital where the ICU is a 28-bed "closed format" department in which medical/surgical patients, including cardiothoracic and neurosurgical patients, are being treated. The GH is an affiliated teaching hospital where the ICU is a 10-bed "closed format" department. The MCL is a large general teaching hospital in the north of The Netherlands, with a 14-bed "closed format" mixed medical / surgical ICU, including cardiothoracic patients.

Patients and data collection

Between January 2006 and March 2007 a total of 340 patients, all 18 years or older, with a clinical indication for a central venous catheter (CVC) [BD Medical Systems, Singapore], pulmonary artery catheter (PAC) [Edwards Lifesciences LLC, Irvine, CA, USA] or Continuous Cardiac Output (CCO) catheter [Arrow Deutschland GmbH, Erding, Germany] (which measures SvO_2 continuously) were recruited. Indication for a central venous, PAC or CCO catheter was left to the discretion of the attending physician. The patients arrived at the ICU either directly from the ED, from the general ward, or after acute surgery with severe sepsis, septic shock or cardiogenic shock, respiratory failure, central nervous problems, and

other acute conditions. In the EDs there was no standardized protocol for hemodynamic treatment of septic patients. Fluid resuscitation was mostly guided by blood pressure monitoring. Inotropes were given scarcely at our EDs. Intubation on the ED was also uncommon. In the operating theatres no $ScvO_2$ / SvO_2 measurements took place, nor any kind of goal directed therapy was implemented. All patients were treated according to standard practice for the ICU. Exclusion criteria were elective surgery and age < 18 years. Collecting data for observational study without informed consent was approved by the Medical Ethics Committees of all 3 hospitals.

Measurements of systolic arterial pressure (SAP), mean arterial pressure (MAP) and central venous pressure (CVP) were recorded immediately after arrival at the ICU. Hematocrit (Hct), lactate plasma levels and pH were determined from the first obtained arterial blood sample at the ICU.

APACHE II-score [12] and SOFA-score [13] at the time of admission at the ICU were collected.

Statistical analysis

The statistical package for the social sciences (SPSS 15.0.1 for Windows) was used for statistical analysis. All data were tested for normal distribution with the Kolmogorov-Smirnov test before further statistical analysis. Differences between both populations were assessed using Student's paired t-test (normally distributed data). Data were displayed as mean ± SD. Statistical significance was assumed at $p < 0.05$.

Results

Patients

A heterogeneous population with a total of 340 critically ill patients was evaluated in the three participating ICUs (table 1). The patients arrived at the ICU either directly from the ED (n=135; 40%), from the general ward (n=126; 37%) or after acute surgery (n=79; 23%). To determine $ScvO_2$ or SvO_2, central venous or mixed venous oxygen saturation was measured as early as possible after insertion of a central venous catheter (n=263) or pulmonary artery / CCO catheter (n=77). The vast majority (93%) of the patients were enrolled within 6 hours after presentation in the ER. More than 99% of all the data was obtained within 2 hours after ICU admission. The numbers of measurements of central or mixed oxygen venous saturation were not normally distributed between the three ICUs. In all three hospitals the mean SvO_2 was higher than 65% and mean $ScvO_2$ was higher than 70%. Overall in-hospital mortality of our population was 32.0%.

In 263 patients venous oxygen saturation was measured centrally (table 2). Mean $ScvO_2$ was 72.0 ± 12.3%. Thirty-eight patients (14%) had a $ScvO_2$ < 60%, and only 14 (5%) patients had a $ScvO_2$ < 50%. While only 1 patient of the latter was in septic shock, in-hospital mortality of these 14 patients was 57% (8/14).

Septic patients

In patients with sepsis or septic shock (n = 150) central venous oxygen was measured in 125 patients and mixed venous oxygen saturation was measured in 25 patients. The in-hospital mortality of our septic patients was 27%. Seventy-three patients arrived at the ICU from the general ward (n=73; 49%). The mean $ScvO_2$ value was normal: 74.0 ± 10.2%. Only eight (6%) patients had a $ScvO_2$ < 60%, and 1 (1%) < 50% (table 2).

Table 1. Distribution of clinical problems in the three ICUs

admission diagnosis	MCL (n=93)	GH (n=138)	AMC (n=109)	total (n=340)
Sepsis/septic shock	47 (51)	64 (46)	39 (36)	150 (44)
Cardiac failure,	28 (30)	36 (26)	31 (28)	95 (28)
cardiac arrest	10	10	17	
Respiratory failure	7 (8)	13 (10)	12 (11)	32 (9)
CNS	5 (5)	7 (5)	10 (9)	22 (7)
Other	6 (6)	18 (13)	17 (12)	41 (12)

Data are presented as numbers (percentage); CNS, central nervous system; MCL, Medical Center Leeuwarden; GH,Gelre Hospital; AMC, Amsterdam Medical Center.

Comparison with the EGDT population [8]

Compared to the Rivers study group our septic patients revealed a significantly higher $ScvO_2$ (74.0 ± 10.2 vs 48.9 ± 12.3%; $p < 0.01$), lower lactate plasma levels (2.7 ± 2.2 vs. 7.3 ± 4.6 mmol/L; $p < 0.01$), and lower hematocrit (30.3 ± 6.9 vs. 34.7 ± 8.5%; $p < 0.01$). Eighty-three percent (83%) needed endotracheal intubation versus 55% in the EGDT study. APACHE II-scores were equal (20.9 ± 7.0 vs. 20.9 ± 7.2; $p = 1.0$). The in-hospital mortality of this subgroup was 26% (table 2).

Mixed venous oxygen saturation

Measurement of mixed venous oxygen saturation took place in 77 patients. Mean SvO_2 was 68.2 ± 11.8%. Mean lactate was 4.3 ± 4.2 mmol/l; arterial pH was 7.30 ± 0.11. With mean APACHE II scores of 21.8 ± 7.3 and mean SOFA scores of 9.3 ± 3.6, the in-hospital mortality was 37% (table 3).

Table 2. Demographic data, variables and outcome data. Comparisons of sepsis patients with EGDT-study [8] data

variable	present cohort (n=263)	sepsis (n=125)	EGDT-study (n=263)	P value[a,b]
age (yr)	67.3 ± 14.2	68.9 ± 13.5	65.7±17.2	0.01*
sex (%)				
female	41	38	49.4	
male	59	62	50.6	
heart rate (beats/min)	107 ± 27	115 ± 26	115 ± 29	1.0
CVP (mmHg)	9.8 ± 5.4	10.8 ± 4.9	5.7 ± 8.5	<0.01*
MAP (mmHg)	58 ± 16	60 ± 13	75 ± 25	<0.01*
$ScvO_2$ (%)	72.0 ± 12.3	74.0 ± 10.2	48.9 ± 12.3	<0.01*
lactate (mmol/l)	3.3 ± 3.3	2.7 ± 2.2	7.3 ± 4.6	<0.01*
arterial pH	7.33 ± 0.12	7.35 ± 0.10	7.32 ± 0.18	0.42
hematocrit (%)	31.0 ± 7.0	30.3 ± 6.9	34.7 ± 8.5	<0.01*
APACHE II score	21.5 ± 8.5	20.9 ± 7.3	20.9 ± 7.2	1.0
SOFA score	9.5 ± 3.6	9.6 ± 3.0		
in-hospital mortality (%)	31.0	26.0		
standard therapy			46.5	
EGD therapy			30.5	

Data are presented as means ± SD. [a] Unpaired T-test, [b] sepsis subgroup vs. EGDT study. * Statistically significant difference. CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation.

Of the 25 patients in whom mixed venous oxygen saturation was measured in the subgroup of septic patients, four (16%) patients showed a SvO_2 value <60% on admission. One patient (4%) had a SvO_2 <50%. In this relatively small subgroup mean Hct was 28.2 ± 5.4%, mean MAP 61.0 ± 13.4 mmHg and mean CVP 13.7 ± 4.6 mmHg, while 80% (20/25 patients) needed mechanical ventilation. Mean APACHE II score was 22.2 ± 5.4 and mean SOFA score10.3 ± 3.7. The in-hospital mortality of this subgroup was 28% (table 3).

Table 3. Demographic data, variables and outcome data; mixed venous saturations

Variable	**present cohort (n=77)**	**sepsis (n=25)**
age (yr)	61.7 ± 14.0	65.4 ± 10.4
sex (%)		
female	39	52
male	61	48
heart rate (beats/min)	102 ± 21	102 ± 21
CVP (mmHg)	13.0 ± 4.9	13.7 ± 4.6
MAP (mmHg)	61 ± 15	61 ± 13
SvO_2 (%)	68.2 ± 11.8	72.1 ± 10.8
lactate (mmol/l)	4.3 ± 4.2	3.3 ± 2.3
arterial pH	7.30 ± 0.11	7.32 ± 0.08
hematocrit (%)	29.9 ± 7.1	28.2 ± 5.4
APACHE II score	21.7 ± 7.3	22.2 ± 5.4
SOFA score	9.3 ± 3.6	10.3 ± 3.7
in-hospital mortality (%)	37.0	28.0

Data are presented as means ± SD. CVP, central venous pressure; MAP, mean arterial pressure; SvO_2, mixed venous oxygen saturation.

Discussion

The main result of this present multicenter observational study is the low incidence of low $ScvO_2$-values (<50%) in septic patients being only 1%. Secondary findings are the normal mean $ScvO_2$ values and normal mean SvO_2 values in critically ill patients, including patients with severe sepsis or septic shock, on admission in the three ICUs.

Development to severe sepsis and septic shock involves several pathogenic changes, including global tissue hypoxia as a result of circulatory abnormalities [14]. Especially hemodynamic optimization as a therapeutic target has been studied over the last decade [2,8,9,15,16]. Based on promising results of earlier studies [2], Rivers *et al.* randomized patients with severe sepsis or septic shock to standard therapy or EGDT. The latter resulted in an absolute reduction in 28-day mortality of 16% [8]. Improvement of the balance between oxygen delivery (DO_2) and oxygen demand (VO_2) played an important role. Other studies however found no reduction of morbidity or mortality as a result of aggressive hemodynamic optimization, despite higher central venous oxygenation or lower lactate concentrations [15,16]. Studies that enrolled patients admitted at the ICU were unable to show decrease in mortality after aggressive hemodynamic optimization [16,17], in contrast to studies that implemented certain treatment protocols, including antibiotic therapy, at the emergency department [8,9,11]. In this ICU study we found mean $ScvO_2$ and SvO_2 values in the normal range. Similar figures are described previously in the later stage of sepsis and in ICU patients [18,19]. This is in concordance with the findings by Gattinoni *et al*.(67,3-69,7%) [15] and Bracht *et al*. (70%) [20].

$ScvO_2$ is a surrogate for SvO_2: a significant correlation between the two has been described[21]. Although it might still be debatable whether central venous and mixed venous oxygen saturation are equivalent or not [18,19,21], the clinical importance of both measurements seems not to be an issue. The Surviving Sepsis Campaign recognizes such

in the resuscitation portion of its severe sepsis and septic shock bundle [1]. Our study design does not allow any statistical evaluation of $ScvO_2$ compared to SvO_2.

APACHE II-scores were similar in comparison to the population described in the EGDT study [8]. This suggests equal mortality rate predictions. However, physiologic scores such as APACHE II are dependent on variables that reflect the progression or reversal of organ dysfunction. Treatment in the ED or operating theatre prior to ICU admission influences calculation of the physiologic scores. Consequently, the physiologic scores at our ICUs could partially be underestimated. The significantly higher lactate plasma levels in the EGDT study suggests a more severe tissue hypoperfusion in that group. However, it is the clearance rate that is associated with less organ failure and improved survival [22].

Unlike significantly lower mean arterial pressures, the higher CVP and the lower hematocrit suggest that the septic patients were less hypovolemic compared to the EGDT population. Relatively high mean blood pressure in the EGDT population suggests an earlier stage of sepsis with predominating vasoconstriction, or pre-existing hypertension. The higher CVP in the subgroup with septic patients (n = 125) is partially the result of high percentage of endotracheal intubation and thus increased intrathoracic pressure before measurement (83%). In the EGDT study less than 55% needed intubation at admission.

As mentioned earlier, in the present study the patients were treated in the ED, or elsewhere, before admission at the ICU. This treatment was different from the treatment given in the EGDT study. Nevertheless, our patients received some fluid therapy. Transfusion of red blood cells in our EDs was based on clinical suspicion or evidence of severe blood loss and not on low hematocrit only. Also, a main principle of treatment is to improve oxygen delivery and this could contribute to higher $ScvO_2$ values in the ICU population compared to the patients described in the EGDT study and other ED studies. Other interventions such as sedation and analgesia, most often to facilitate endotracheal intubation and ventilation might have been beneficial for the balance between oxygen

delivery and oxygen demand. Also the trend of changing $ScvO_2$- and other physiological values, influencing outcome [23,24], is not taken into account in our study. Of course, all these factors are important differences between ER populations and ICU populations, but are not predominating. We are aware that comparison between those populations is limited by the abovementioned differences.

As a result from the study design, statements about cut-off $S(c)vO_2$ values for outcome prediction [20,24] or impact on therapeutic intervention, are not possible. Also, we did not look at the use of vital signs as indicator of tissue oxygenation in comparison to mixed or central venous saturation. Lack of clear insight of treatment and time spent at the different EDs, operating theatres or wards is a limitation of our study as well. Nevertheless, since we also aimed at the usefulness of measuring $ScvO_2$ or SvO_2 on ICU admission, we think these factors are not pertinent to the results. For example, Bracht *et al.* [20] found no correlation between $ScvO_2$ values and length of hospital stay before unplanned ICU admission.

Comparing our sepsis population with the ED population described in the important study by Rivers [8] is purely ment to be illustrative. Obviously, as we described, there are differences between ED and ICU populations in general. But there are also, depending on geographical setting, important differences between populations and health care systems. And so, we subscribe to the view of Ho *et al.* [25] that the syndrome described in the EGDT trial may be relatively uncommon depending on geographical setting and health care system. However, this does not undermine the importance of early identification of patients at high risk for cardiovascular collapse. For example, in our study of the fourteen patients with a $ScvO_2 < 50\%$ the in-hospital mortality was 57%.Finally, the in-hospital mortality in our study was 32.0% for the total population and 27.0 % for the patients with severe sepsis or septic shock. Again this reflects recent findings by others: Ho *et al*. (30.2%) [25] and Shapiro *et al.* (26.9%) [26].

In conclusion, the incidence of low $ScvO_2$ values on acutely admitted critically ill patients is low in Dutch ICUs. This is especially true for patients with sepsis / septic shock.

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References

1. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, marshall J, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; for Surviving Sepsis Campaign: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**:858-873.
2. Rady MY, Rivers EP, Novak RM: Resuscitation of the critically ill in the ED: **responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate.** *Am J Emerg Med* 1996, **14**: 218-225.
3. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B: **Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units; French ICU Group for Severe Sepsis**: *JAMA* 1995, **274**: 968-974.
4. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J: **A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients.** *Anesth Analg* 2000, **90**: 1052-1059.
5. Kasnitz P, Druger Gl, Yorra F, Simmons DH: **Mixed venous oxygen tension and hyperlactataemia. Survival in severe cardiopulmonary disease**. *JAMA* 1976, **236**: 570-574.
6. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF: **Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined eve**nts. *Chest* 1993, **103**: 900-906.
7. Edwards JD: **Oxygen transport in cardiogenicand septic shock**. *Crit Care Med* 1991, **19**: 658-663.
8. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; for the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**: 1368-1377.
9. Shapiro NI, Howell MD, Talmor D, Lahey D, Ngo L, Buras J, Wolfe RE, Weiss JW, Lisbon A: **Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol**. *Crit Care Med* 2006, **34**: 1025-1032.

10. Trzeciak S, Dellinger RP, Abate NL, Cowan RM, Strauss M, Kilgannon H, Zanotti S, Parrillo JE: **A 1-year experience with implementing Early Goal-Directed Therapy for septic shock in the emergency department**. *Chest* 2006, **129**: 225-232.

11. Kortgen A, Niederprüm, Bauer M: **Implementation of an evidence-based "standard operating procedure"and outcome in septic shock**. *Crit Care Med* 2006, **34**:943-949.

12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system**. *Crit Care Med* 1985, **13**: 818-829.

13. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: **The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine**. *Intensive Care Med.* 1996, **22**: 707–710.

14. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP: **The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study.** *JAMA* 1995, **273**: 117-123.

15. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R – SvO_2 collaborative group: **A trial of goal-oriented hemodynamic therapy in critically ill patients**. *N Engl J Med* 1995, **333**: 1025-1032.

16. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D: **Elevation of systemic oxygen delivery in the treatment of critically ill patients**. *N Engl J Med* 1994, **330**: 1717-1722.

17. Krafft P, Steltzer H, Hiesmayr, Klimscha, Hammerle AF: **Mixed venous oxygen saturation in critically ill septic shock patients: The role of defined events**. *Chest* 1993, **103**: 900-906.

18. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM: **Comparison of ventral-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand.** *Chest* 1989, **95**: 1216-1221.

19. Varpula M, Karlsson S, Ruokonen E, Pettila V: **Mixed venous oxygen saturation cannot be estimated by cantral venous oxygen saturation in septic shock**. *Intensive Care Med* 2006, **32**: 1336-1343.

20. Bracht H, Hängi M, Jeker B, Wegmüller N, Porta F, Tüller D, Takala J, Jakob SM: **Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary ICU: an observational study**. *Crit Care* 2007, **11**: R2-R9.

21. Reinhart K, Kuhn H-J, Hartog C, Bredle DL: **Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill**. *Intensive Care Med* 2004, **30**: 1572-1578.

22. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC: **Early lactate clearance is associated with improved outcome in severe sepsis and septic shock.** *Crit Care Med* 2004, **32**: 1637-1642.

23. Collaborative Study Group on Perioperative $ScvO_2$ monitoring: **Multicentre study on peri- and postoperative central venous oxygen saturation in high-risk surgical patients**. *Crit Care* 2006, **10**: R158-165.

24. Pearse RM, Dawson D, Fawcett J, Rhodes A, Grounds M, Bennett ED: **Changes in central venous saturation after major surgery, and association with outcome**. *Crit Care* 2005, **9**: R694-R699.

25. Ho BCH, Bellomo R, McGain F, Jones D, Naka T, Wan L, Braitsberg G: **The incidence and outcome of septic shock patients in the absence of early-goal directed therapy.** *Crit Care* 2006, **10**: R80.

26. Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW: **Mortality in Emergency Department Sepsis (MEDS) score: A prospectively derived and validated clinical prediction rule**. *Crit Care Med* 2003, **31**: 670-675.

Chapter 3

Relation between mixed venous and central venous saturation in sepsis: no influence of sepsis origin

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Abstract

Introduction We tested the hypothesis that central venous saturation ($ScvO_2$) does not reliably predict mixed venous saturation (SvO_2) in sepsis. Additionally we looked at the influence of the source (splanchnic or non-splanchnic) of sepsis on this relation.

Methods We concurrently determined $ScvO_2$ and SvO_2 in a group of 53 patients with severe sepsis during the first 24 hours after admission to the intensive care units in 2 Dutch hospitals. We assessed correlation and agreement of $ScvO_2$ and SvO_2., Additionally, we compared the mean differences between $ScvO_2$ and SvO_2 of both splanchnic and non-splanchnic group.

Study Design Prospective observational two-center study.

Results A total of 265 paired blood samples were obtained. $ScvO_2$ overestimated SvO_2 by less than 5% with wide limits of agreement. For changes in $ScvO_2$ and SvO_2 results were similar. The distribution of the difference ($ScvO_2$ - SvO_2) (< 0 or ≥ 0) was similar in survivors and nonsurvivors. The mean ($ScvO_2$ - SvO_2) in the splanchnic group was similar to the mean ($ScvO_2$ - SvO_2) in the non-splanchnic group (0.8 ± 3.9% vs. 2.5 ± 6.2 %; p = 0.30). Oxygen extraction ratio (O_2ER; p=0.23) and its predictive value for outcome (p=0.20) was similar in both groups.

Conclusions $ScvO_2$ does not reliably predict SvO_2 in patients with severe sepsis. The trend of $ScvO_2$ is not superior to the absolute value in this context. A positive difference ($ScvO_2$ - SvO_2) is not associated with improved outcome.

Introduction

Global tissue hypoxia as a result of systemic inflammatory response or circulatory failure is an important indicator of serious illness preceding multiple organ failure. The development of organ failure predicts outcome of the septic patient [1]. Unrecognized and untreated global tissue hypoxia increases morbidity and mortality: decreased mixed venous saturation (SvO_2) values predict poor prognosis in septic shock [2-4].

Controversy however remains: there is no clear evidence that guiding hemodynamic optimization by monitoring central venous saturation ($ScvO_2$) or SvO_2 is useful in all patients with sepsis or septic shock, especially in intensive care unit (ICU) setting. The controversy includes their interchangeability [5,6].

Also, in patients with a splanchnic cause of sepsis, $ScvO_2$ may be normal, while the SvO_2 may be decreased due to elevated metabolic demand. On the other hand, due to sepsis related vasodilatation, also in the digestive tract, leading to diminished oxygen consumption, mixed venous saturation may be normal [7]. This could mean that the 5% difference between $ScvO_2$ and SvO_2 is not as consistent in sepsis as postulated earlier [8,9]. Nevertheless, recently an association between a positive gradient O_2 gradient ($ScvO_2 – SvO_2 \geq 0$) and ICU survival in critically ill patients was described [10]. Therapy aimed at increasing this gradient is could mean improved survival. However, this demands measurement of both $ScvO_2$ and SvO_2.

We tested the hypothesis that $ScvO_2$ does not reliably predict SvO_2 in sepsis, i.e. a consistent 5% difference between $ScvO_2$ and SvO_2 does not exist. We also looked at the possible relationship between a positive difference between $ScvO_2$ and SvO_2 ($ScvO_2 - SvO_2$) and ICU survival. In a secondary analysis we tested the hypothesis whether the relationship between $ScvO_2$ and SvO_2 is independent of sepsis origin or not.

Methods

Setting

We studied ICU populations in two teaching hospitals. The Martini Hospital [Groningen, The Netherlands] (MH) where the ICU is a 14-bed “closed format” mixed medical / surgical ICU department and The Medical Center Leeuwarden [Leeuwarden, The Netherlands] (MCL) where the ICU is a 16-bed “closed format” mixed medical / surgical ICU, including cardiothoracic patients. The study was approved by both Local Ethics Committees. Informed consent was obtained in all cases from the patient or from the patient’s legal representative.

Patients and data collection

This prospective observational study included patients, all 18 years or older, with sepsis or septic shock according to international criteria [11], between January and September 2009. Only patients were included in whom there was a clinical indication for additional hemodynamic monitoring using a pulmonary artery catheter (PAC) [Criticath SP 5507H TD, Becton Dickinson, Singapore] or a Continuous Cardiac Output (CCO) catheter [Arrow Deutschland GmbH, Erding, Germany]. The catheter was inserted into an internal jugular vein or subclavian vein according to standard procedure. Position was confirmed by the presence of pulmonary artery pressure tracings and chest radiography. No complications other than transient arrhythmias were observed during the insertion of any catheter. Primary data, including hemodynamic parameters, were collected at 6-hour interval (T0, T1, T2, T3, T4) during the first 24 hours after acute ICU admission. Standard blood samples of 2 ml were drawn simultaneously from distal (pulmonary artery; PA) and proximal / side portal (superior caval vein; SCV) from PAC or CCO catheter. To avoid falsely high readings due to aspiration of pulmonary capillary blood, aspiration was done gently to avoid high negative pressure

when blood samples were taken. We took blood from the proximal port of the catheter as representative of central venous blood [6,8,10]. We did not use any continuously measured values of the catheter itself in the cases where a CCO catheter was used. Only patients with a complete series of 5 paired measurements were finally included. Also, arterial blood samples were obtained, including serum lactate. All blood samples were analyzed by a co-oximeter (Radiometer ABL800 flex, Copenhagen, Denmark). The Acute Physiology, Age and Chronic Health Evaluation (APACHE) II-score after 24 hours of ICU admission was collected [12].

Statistical analysis

Analysis was done for the total population and for secondary analysis the population was divided into two groups: patients with splanchnic source of sepsis and patients with a non-splanchnic source of sepsis. We calculated a sample size of 200 paired samples to detect an absolute difference between $ScvO_2$ and SvO_2 in a two-sided test with a 0.05 type I error and a 95% probability in case of standard deviation of 10% [13,14]. Statistical tests were two-tailed and performed by the statistical package for the social sciences (SPSS 16.0.1 for Windows, Chicago, IL, USA) or MedCalc software (version 11.2.1, Mariakerke, Belgium), the latter for comparing ROC curves. GraphPad software (Prism 5.0, La Jolla, CA, USA) was used for graphics. Measurements were not independent but clustered within each patient. All data were tested for normal distribution with the Kolmogorov-Smirnov test before further statistical analysis. Differences between both groups were assessed using Student's t-test in case of normal distribution or χ^2 test. For each time point, T0 toT4, ($ScvO_2$ - SvO_2) was calculated including the average difference per patient. The agreement between absolute values of $ScvO_2$ and SvO_2 and the agreement of the changes of these values were assessed by the mean bias and 95% limits of agreement (mean bias ± 1.96 x standard deviation) as described by Bland and Altman [15]. χ^2 test was used to establish significance

between the number of survivors and non-survivors. Spearman correlations for assessing possible factors affecting ($ScvO_2$ - SvO_2) were determined: at each time point ($ScvO_2$ - SvO_2) was compared to hemodynamic and perfusion variables.

For secondary analysis we also calculated the mean ($ScvO_2$ - SvO_2) per group and they were compared using Student's unpaired t-test. Additionally, the influence on outcome of O_2ER was determined because ($ScvO_2$ - SvO_2) did correlate with O_2ER in the secondary analysis. SvO_2 and arterial oxygen saturation (SaO_2) were used in the calculation of the systemic oxygen extraction ratio (O_2ER). Receiver Operating Characteristic (ROC) curves were used for the assessment of sensitivity and specificity of O_2ER in predicting in-hospital mortality. Data were displayed as mean ± SD. Statistical significance was assumed at $p < 0.05$.

Results

We enrolled 56 patients, of whom three patients were excluded due to lack of data (technical problems). We evaluated data from 53 patients with sepsis. Altogether 265 paired blood samples were obtained. Baseline characteristics and outcome of the total population and both groups are shown in table 1. Length of stay at the ICU (LOS_{ICU}) was 12 ± 10 days and length of stay at the hospital (LOS_{HOSP}) was 25 ± 18 days.

Table 1. **Baseline characteristics and outcome**

variable	total population (n=53)	splanchnic (n=25)	non-splanchnic (n=28)	P value[#]
age (yr)	66 ±12	66 ± 12	66 ± 13	0.46
CVP (mmHg)	12 ± 6	11 ± 5	14 ± 6	0.06
MAP (mmHg)	66± 10	65± 12	66 ± 9	0.65
$ScvO_2$ (%)	72.0 ± 10.0	73.7 ± 10.5	70.6 ± 9.6	0.29
SvO_2 (%)	71.8± 10.6	75.2± 9.9	68.6 ± 10.5	0.03*
lactate (mmol/L)	3.5 ± 3.5	3.8± 3.8	3.5 ± 3.2	0.33
arterial pH	7.30± 0.10	7.29 ± 0.10	7.29 ± 0.12	0.43
hematocrit (%)	30.1± 5.7	30.2 ± 6.1	32.1 ± 5.7	0.59
APACHE II	26.6 ± 7.6	25.3 ± 7.3	28.7 ± 7.8	0.24
hospital mortality (%)	26.5	29.2	24.0	0.56

Data are presented as means ± SD or as numbers. [#] splanchnic group vs. non-splanchnic group. CVP, central venous pressure; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; APACHE II, acute physiology, age and chronic health evaluation; * statistically significant difference

The $ScvO_2$ overestimated the SvO_2 by a mean bias (or absolute difference) of 1.7% ± 7.1% in the total population. The 95% limits of agreement were wide (-12.1% to 15.5%; Figure 1A). Figure 2 illustrates this: mean $ScvO_2$ and mean SvO_2 values are shown at each time point. Results at time point T=0 and at different time points were similar, including wide limits of agreement (data and plots not shown). Bias between changes of $ScvO_2$ and SvO_2 was 0.6% ± 7.1% in the total population with 95% limits of agreement of -13.4% to 14.6%; Figure 1B. Results were similar at time point T=0 and at different time points, including wide limits of agreement (data and plots not shown).

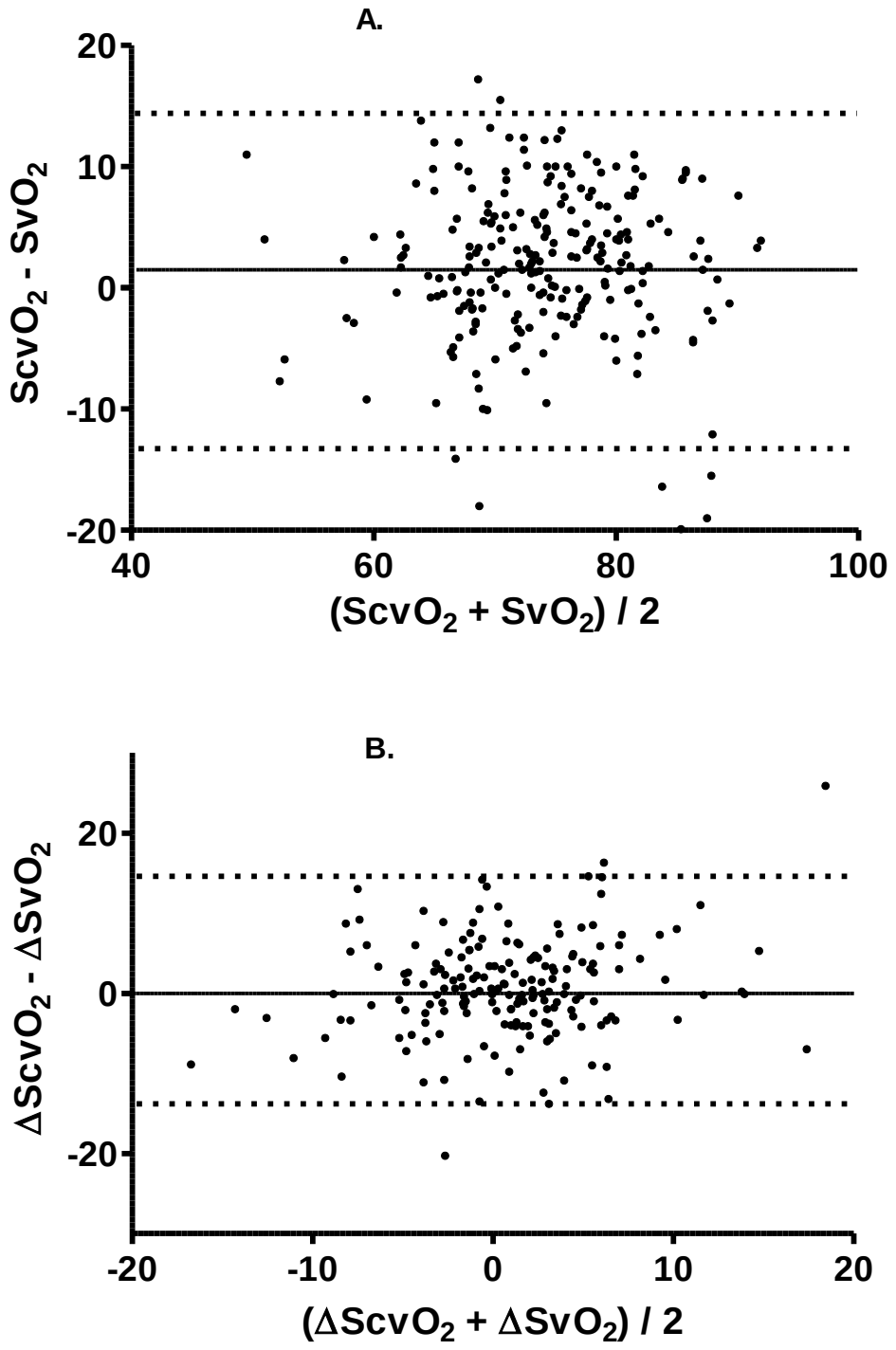


Figure 1. Bland and Altman plot showing the agreement between A. $ScvO_2$ and SvO_2 (bias 1.7, 95% limits of agreement from -12.1 to 15.5) and in B. changes in $ScvO_2$ and SvO_2 (bias 0.6, 95% limits of agreement from -13.4 to 14.6).

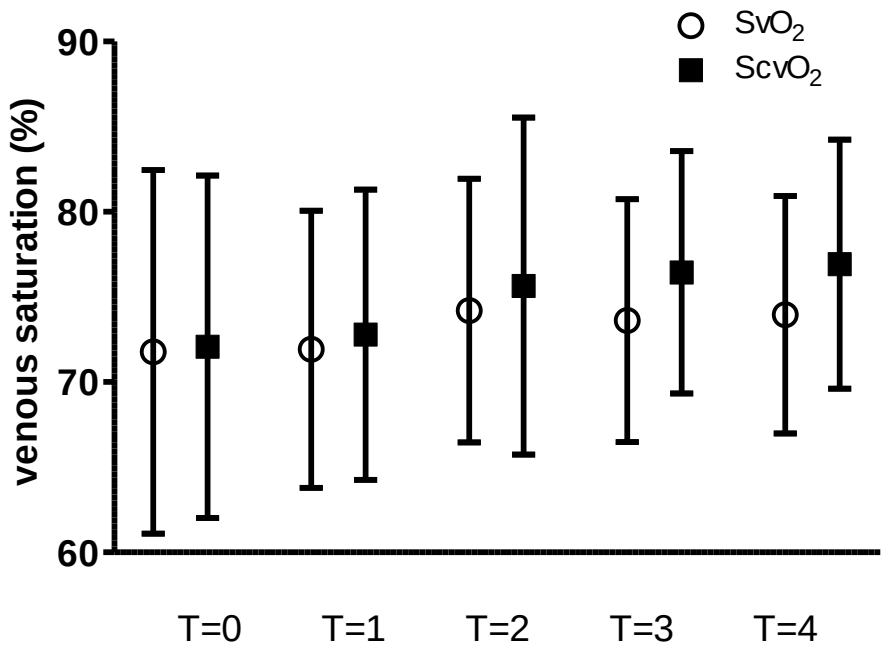


Figure 2. Mean SvO_2 and $ScvO_2$ values at different time points. $ScvO_2$ is consistently higher than SvO_2 without statistical difference (paired t-test; all $p > 0.05$).

Differences between survivors and nonsurvivors

As $ScvO_2$ of 70% has been used as a target for guided therapy in septic patients [4], we evaluated the frequencies of $ScvO_2$ values below 70% in both survivors and nonsurvivors. Of all $ScvO_2$ measurements in survivors 15% fell below 70%, whereas in nonsurvivors 47% of all $ScvO_2$ measurements fell below 70% ($p < 0.01$).

Assuming a 5% difference between $ScvO_2$ and SvO_2 [1], we also evaluated the frequencies of SvO_2 values below 65% in both survivors and nonsurvivors. Of all measurements in survivors 7% fell below 65%, whereas in nonsurvivors 27% of all SvO_2 measurements fell below 65% ($p < 0.01$).

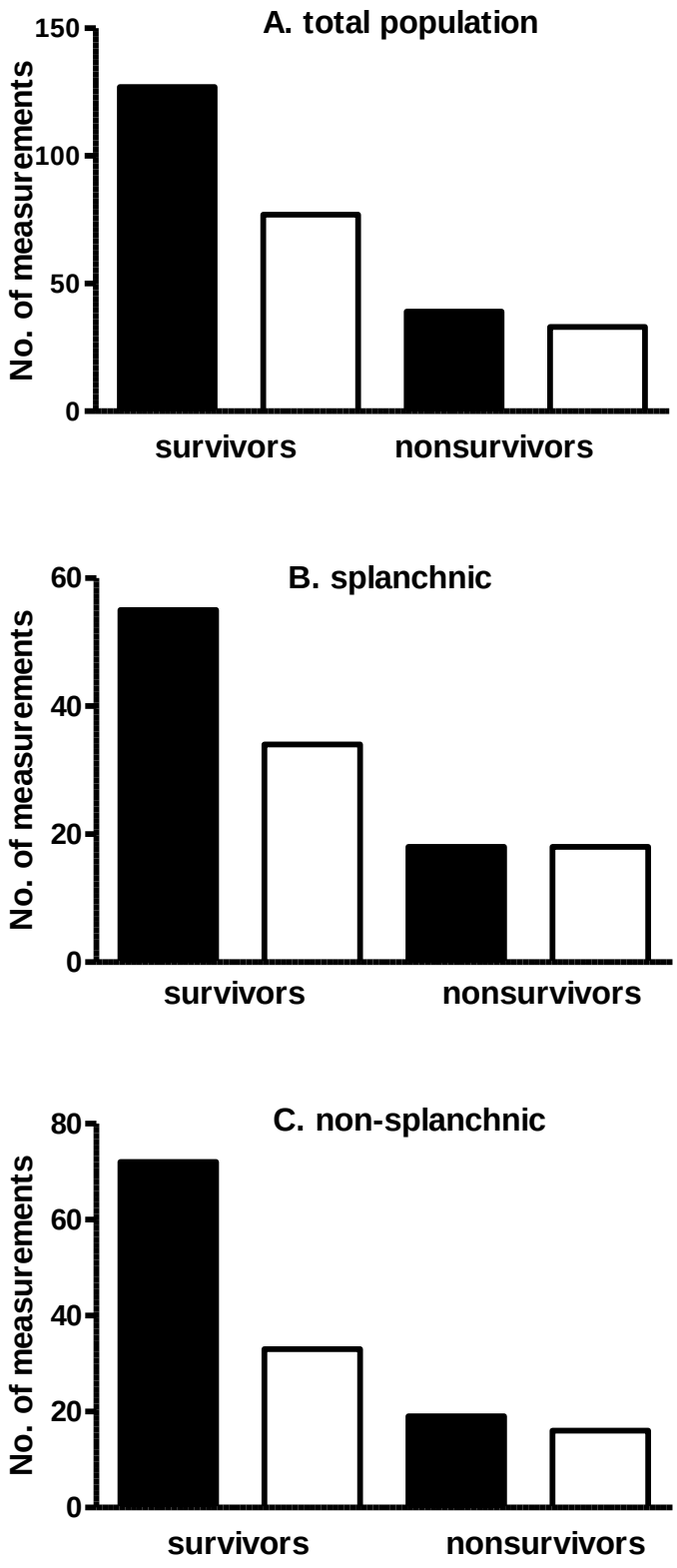


Figure 3. Number of paired measurements resulting in either a ($ScvO_2$ – SvO_2) ≥0 (black bars) or in a ($ScvO_2$ – SvO_2) <0 (white bars). There was no significant different distribution of ($ScvO_2$ – SvO_2) between survivors and non-survivors.

Figure 3 shows the number of paired measurements resulting in either a ($ScvO_2$ - SvO_2)≥0 or in a ($ScvO_2$ - SvO_2) <0. There was no significant different distribution of ($ScvO_2$ - SvO_2) between survivors and non-survivors in the total population (p=0.13), splanchnic group (p=0.23) or non-splanchnic group (p=0.13).

Influence on difference between $ScvO_2$ and SvO_2 ($ScvO_2$ – SvO_2)

The difference between $ScvO_2$ and SvO_2 was dependent on the level of $ScvO_2$ when values of <60%, 60-70%, 70-80% and >80% were analyzed separately. The mean ($ScvO_2$ - SvO_2) were 8.9%, 1.0%, 2.4%, and 4.2%, respectively. Due to low incidence (4.9%) of low $ScvO_2$ values (< 60%) we did not assess statistics on these differences. Assessment of Spearman correlation coefficients did not show any relation between cardiac output (CO), cardiac index (CI), dopamine (µg/kg/min), norepinephrine (µg/kg/min), mean arterial blood pressure, arterial saturation, hemoglobin, hematocrit, pH, or lactate levels and ($ScvO_2$ - SvO_2) (all $p > 0.05$). O_2ER correlated significantly with ($ScvO_2$ - SvO_2) at all time points (all $p < 0.01$).

Differences between groups

Secondary analysis showed that twenty-five patients presented with splanchnic source of sepsis and 28 patients presented with a non-splanchnic source of sepsis. Thirty patients (15 splanchnic / 15 non-splanchnic) were enrolled in the MCL and 23 (10 splanchnic / 13 non-splanchnic) patients were enrolled in the MH.

The sources of sepsis in the non-splanchnic group were mainly pneumonia (n = 16; 57%) and infection of the urogenital tract (n = 5; 18%). Other sources were meningitis, arthritis, epiglottitis, endocarditis, and infected soft tissue.

At baseline, SvO_2 (75.2 ± 9.9% vs. 68.6 ± 10.5%; p = 0.03) was different between groups. There was no significant difference between the mean ($ScvO_2$ - SvO_2) of both groups: splanchnic, 0.8 ± 3.9% vs. non-splanchnic, 2.5 ± 6.2 % (p = 0.30).

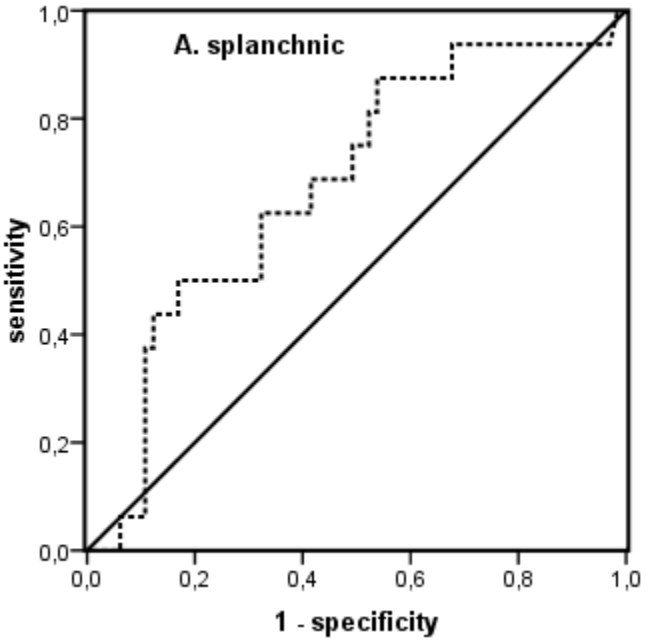
Bias between $ScvO_2$ and SvO_2 was 0.7% ± 6.3% (95% limits of agreement of -11.7% to 13.1%) in the splanchnic group and 2.6% ± 7.5% (95% limits of agreement of -12.2% to 17.4%) in the non-splanchnic group. Bias between changes in $ScvO_2$ and SvO_2 was 0.9% ± 7.9% (95% limits of agreement of -14.5% to 16.3%) in the splanchnic group and 0.3% ± 6.5% (95% limits of agreement of -12.4% to 13.0%) in the non-splanchnic group; plots not shown.

The difference between $ScvO_2$ and SvO_2 was dependent on the level of $ScvO_2$ when values of <60%, 60-70%, 70-80% and >80% were analyzed separately. The mean ($ScvO_2$ - SvO_2) were 12.3%, 2.1%, 1.0%, 4.3% for the splanchnic group; 4.6%, 0.1%, 3.8%, and 4.7% for the non-splanchnic group.

There was no significant different distribution of ($ScvO_2$ - SvO_2) between survivors and non-survivors in both the splanchnic group (p=0.23) and the non-splanchnic group (p=0.13); Figure 4.

Oxygen extraction ratio (O_2ER)

The O_2ER in the splanchnic group was similar to the O_2ER in the non-splanchnic group (0.23 ± 0.07 vs 0.24 ± 0.09; p=0.23). Figure 4 shows the ROC curves of O_2ER for the splanchnic and non-splanchnic group. Optimal value of O_2ER was 0.22 (sensitivity = 0.46, specificity = 0.87) for the non-splanchnic group and 0.31 (sensitivity = 0.85, specificity 0.40) for the splanchnic group. These curves represent the reliability of the O_2ER as predictor of in-hospital mortality. Area under the curve (AUC) in the splanchnic group was not significantly larger than the AUC in the non-splanchnic group (0.67 vs. 0.55; p=0.20).



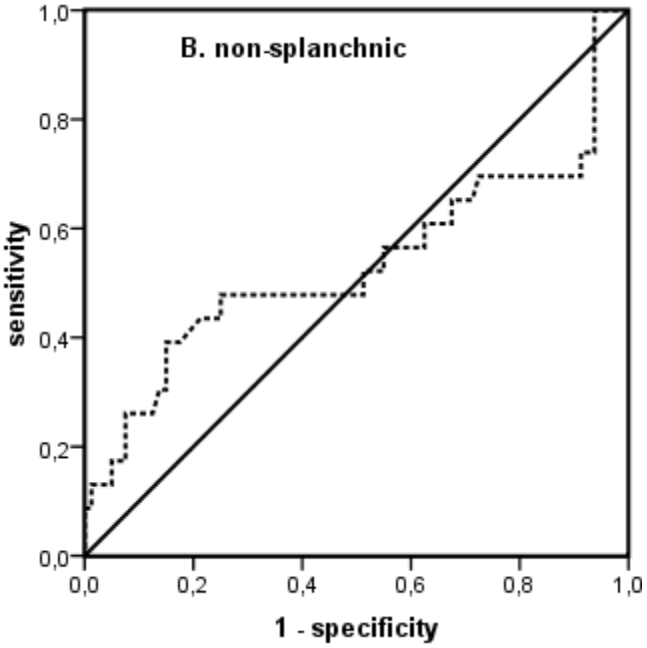


Figure 4. ROC curves of O_2ER for the splanchnic and non-splanchnic group. AUC in the splanchnic group (A) was not significantly larger than AUC in the non-splanchnic group (B) (0.67 vs. 0.55; p=0.20).

Discussion

We could confirm our hypothesis that $ScvO_2$ does not reliably predict SvO_2 in patients with severe sepsis: the agreement of $ScvO_2$ and SvO_2 was clinically not adequate. The difference between $ScvO_2$ and SvO_2 varied according to the level of $ScvO_2$, being the greatest in low (<60%) and high ranges (>80%). In patients with severe sepsis or septic shock the difference between $ScvO_2$ and SvO_2 appears not to be a fixed one and does not seem to be predictive for in-hospital mortality. Finally, the difference between $ScvO_2$ and SvO_2 is independent of several hemodynamic variables, with exception of O_2ER.

The bias was small with $ScvO_2$ being consistently larger than SvO_2. However, this consistent bias also implies a greater relative error for SvO_2 values at lower $ScvO_2$ values. Additionally, the wide limits of agreement between $ScvO_2$ and SvO_2 are unacceptably wide and independent of time point. The widely assumed 5% difference between $ScvO_2$ and SvO_2 [1,8,9] seems not consistent in patients with severe sepsis or septic shock. A variety of factors influence the difference between both variables in patients with sepsis: mixing of the less saturated blood from the coronary sinus in the right atrium, sepsis related vasodilatation, heterogeneity of flow within and between organs, and decreased cerebral oxygen uptake during sedation. Based on the present study, the net effect of these factors seems unpredictable. Our results seem concordant with earlier findings [6,8,16]. The first study described a small heterogeneous group of patients with septic shock. $ScvO_2$ was consistently higher than SvO_2 and the limits of agreement were equally wide. Moreover, the difference between $ScvO_2$ and SvO_2 varied according to the level of $ScvO_2$ and deviated in the extreme ranges ($60\% < ScvO_2 > 80\%$) [6]. The lower range (venous saturations < 60%) is clinically of the greatest interest because the patients admitted with such low venous saturations are the ones who could possibly benefit from $ScvO_2$ -guided therapy [4]. With the results of the present study in mind the clinician should be aware of the large variability between $ScvO_2$

and SvO_2. Clinically important, this large variability was already present on admission (T=0). At this time point the first decisions are made on how to resuscitate and on what goals should be achieved. Such large uncertainty in estimating SvO_2 by $ScvO_2$ is unlikely to be suitable for protocol-guided resuscitation in which decreases in SvO_2 or $ScvO_2$ may trigger therapeutic interventions. Normalization of $ScvO_2$ after resuscitation will not automatically imply normalization of SvO_2.

If the individual values of $ScvO_2$ and SvO_2 do not agree could this be different for the trends of $ScvO_2$ and SvO_2? In anesthetized subjects who underwent elective neurosurgery measurement of oxygen saturations was performed in various hemodynamic conditions. It was concluded that for clinical purposes the trend of $ScvO_2$ might be substituted for the trend of SvO_2 [17]. In the present study however, we found wide limits of agreement between the change of $ScvO_2$ and the change of SvO_2 in critically patients. As for the absolute values of $ScvO_2$ and SvO_2, substitution of the change of $ScvO_2$ for the change of SvO_2 in patients with sepsis is therefore undesirable. This is in concordance with earlier findings in patients with cardiogenic or septic shock: changes in $ScvO_2$ and SvO_2 did not follow the line of perfect agreement and $ScvO_2$ and SvO_2 were not considered to be interchangeable [18].

Another issue is whether a $ScvO_2$ of 70% as treatment goal in sepsis or septic shock after resuscitation may be considered useful. In a study by Reinhart et al. $ScvO_2$ was measured continuously in critically ill patients for an average of 42 hours. More than 87% of the values in nonsurvivors and 95% of the values in survivors were above 70%. This difference was significant. Average time per patient below the cutoff value was twice as long in nonsurvivors [5]. In the present study $ScvO_2$ values in nonsurvivors fell also more frequently below the cutoff value of 70% compared to survivors and SvO_2 values below 65% were more frequently found in nonsurvivors compared to survivors. Our data suggest that after the first hours of resuscitation monitoring of venous oxygen saturations could still be clinically relevant.

More recently, Gutierrez et al. described an association between a positive ($ScvO_2$ – SvO_2), and ICU survival in critically ill patients. A significantly greater number of survivors had a ($ScvO_2$ - SvO_2) ≥0 compared to non-survivors. The difference between $ScvO_2$ and SvO_2 became increasingly positive in survivors from initial to final measurement. They suggested that this might be associated with clinical recovery, perhaps reflecting a greater rate of O_2 utilization [10]. This is in concordance with findings in post-operative cardiac patients which described a similar trend [19]. Although we noted that ($ScvO_2$ - SvO_2) was more frequently positive in survivors, and O_2ER correlated with ($ScvO_2$ - SvO_2) we found no significant difference in distribution of ($ScvO_2$ - SvO_2) between survivors and non-survivors. Our results could not confirm a greater rate of O_2 utilization in survivors as suggested by Gutierrez et al [10]. However, it is possible that the number of measurements in our study was not sufficient enough to detect a difference in distribution of ($ScvO_2$ - SvO_2).

Secondary analysis showed that the inconsistent difference between $ScvO_2$ and SvO_2 is independent of sepsis origin. There was no significant difference between the mean ($ScvO_2$ - SvO_2) of both groups and the limits of agreement were wide for both the absolute values and for the changes in $ScvO_2$ and SvO_2. SvO_2 values were higher in the splanchnic group compared to the non-splanchnic group for a certain $ScvO_2$ value. This phenomenon could be explained by sepsis related vasodilatation in the digestive tract. Despite heterogeneity of flow within and between various organs in patients with splanchnic sepsis [20] this leads to diminished oxygen consumption which results in a relatively higher SvO_2. Apparently, a normal SvO_2 does not rule out the presence of limited oxygen consumption in the splanchnic region [7]. Moreover, we found no difference in O_2ER between the splanchnic and non-splanchnic group. This suggests less oxygen utilization in the digestive tract than could be expected based on the assumption that in all septic patients the difference between $ScvO_2$ and SvO_2 equals 5%.

This study has limitations. First, all patients were sedated, mechanically ventilated, and none of them were in hemorrhagic shock. Our findings may not be generalized to patients less critically ill or those with hemorrhagic shock. Also, due to intubation $ScvO_2$ values could have been relatively high in relation to disease severity [21]. Second, we investigated ICU patients which could mean at a later stage of sepsis; timing of measurements was probably not all in the same stage of critical illness. Third, in this study $ScvO_2$ and SvO_2 values did not change between different time points as a result of a protocolled intervention: conclusions on independence of time point are of limited value. However, measurements took place within individual patients: each subject served as its own control. Finally, we used the proximal port of the used catheters as surrogate of $ScvO_2$. Some $ScvO_2$ measurements might have been influenced due to a more distal location in the right atrium which allows mixing of superior and inferior caval vein blood. Nevertheless, our results are consistent and in concordance with previous studies where a similar technique was used [6,8,10].

Conclusions

We conclude that $ScvO_2$ does not reliably predict SvO_2 in patients with sepsis, independent of sepsis origin. Assuming a consistent 5% difference between $ScvO_2$ and SvO_2 can lead to erroneous clinical decisions. The change of $ScvO_2$ compared to the change of SvO_2 is not more reliable than the exact numerical values in this context. Finally, a positive difference ($ScvO_2$ - SvO_2) is not associated with improved outcome in patients with sepsis. The abovementioned conclusions apply for sepsis originated from both splanchnic and non-splanchnic origin.

References

1. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall J, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; for Surviving Sepsis Campaign: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**: 858-873.
2. Edwards JD: **Oxygen transport in cardiogenic and septic shock**. *Crit Care Med* 1991, **19**: 658-663.
3. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF: **Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events.** *Chest* 1993, **103**: 900-906.
4. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; for the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**: 1368-1377.
5. Reinhart K, Kuhn HJ, Hartog C, Bredle DL: **Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill**. *Intensive Care Med* 2004, **30**: 1572-1578.
6. Varpula M, Karlsson S, Ruokonen E, Pettilä V: **Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock**. *Intensive Care Med* 2006, **32**: 1336-1343.
7. Dahn MS, Lange MP, Jacobs LA: **Central mixed and splanchnic venous oxygen saturation monitoring**. *Intensive Care Med* 1988, **14**: 373-378.
8. Chawla LS, Zia H, Guttierez G, Katz NM, Seneff MG, Shah M: **Lack of equivalence between central and mixed venous oxygen saturation**. *Chest* 2004, **126**: 1891-1896.
9. Rivers E: **Mixed vs central venous oxygen saturation may be not numerically equal, but both are still clinically useful**. *Chest* 2006, **129**: 507-508.
10. Gutierrez G, Comignanni P, Huespe L, Hurtado FJ, Dubin A, Jha V, Arzani Y, Lazzeri S, Sosa L, Riva J, Kohn W, Suarez D, Lacuesta G, Olmos D, Mizdraji C, Ojeda A: **Central venous to mixed venous blood oxygen and lactate gradients are associated with outcome in critically ill patients.** *Intensive Care Med* 2008, **34**: 1662-1668.

11. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: **2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.** *Intensive Care Med* 2003, **29**: 530-538.

12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system**. *Crit Care Med* 1985, **13**: 818-829.

13. Friedman LM, Fuberg CD, DeMets DL: **Fundamentals of clinical trials** (ed 3). New York, NY, Springer-Verlag, 1998, pp 111.

14. van Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk PE, Kuiper MA: **The incidence of low venous oxygen saturation on admission in the ICU: a multicenter observational study in the Netherlands.** *Crit Care* **2008**, 12: R33.

15. Bland JM, Altman DG: **Agreement between methods of measurement with multiple observations per individual**. *J Biopharm Stat* 2007, **17**: 571-582.

16. Martin C, Auffray JP, Badetti C, Perin G, Papazian L, Gouin F: **Monitoring of central venous oxygen saturation versus mixed venous oxygen saturation in critically ill patients**. *Intensive Care Med* 1992, **18**: 101-104.

17. Dueck MH, Klimek M, Appenrodt S, Weigand C, Boerner U: **Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions.** *Anesthesiology* 2005, **103**: 249-257.

18. Ho KM, Harding R, Chamberlain J, Bulsara M: **A comparison of central and mixed venous oxygen saturation in circulatroy failure**. *J Cardiothoracic Vasc Anesth* 2008, doi:10.1053/j.jvca.2007.10.011.

19. Sander M, Spies CD, Foer A, Weymann L, Braun J, Volk T, Grubitzsch H, von Heymann C: **Agreement of central venous saturation and mixed venous saturation in cardiac surgery paients.** *Intensive Care Med* 2007, **33**: 1719-1725.

20. Boerma EC, van der Voort PHJ, Spronk PE, Ince C: **Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis.** *Crit Care Med* 2007, **35**: 1055-1060.

21. Hernandez G, Peña H, Cornejo R, Rovegno M, Retamal J, Navarro JL, Aranguiz I, Castro R, Bruhn A: **Impact of emergency intubation on central venous oxygen saturation in critically patients: a multicenter observational study**. *Crit Care* 2009, **13**: R63.

Chapter 4

Femoral venous oxygen saturation is no surrogate for central venous oxygen saturation

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Abstract

Objective The purpose of our study was to determine if central venous oxygen saturation ($ScvO_2$) and femoral venous oxygen saturation ($SfvO_2$) can be used interchangeably during surgery and in critically ill patients.

Methods We concurrently determined $SfvO_2$ and $ScvO_2$ in a group of 100 stable cardiac patients, which served as control group. Furthermore, we determined simultaneously $SfvO_2$ and $ScvO_2$ in 30 surgical patients and in 30 critically ill patients and evaluated changes over time. Correlation and agreement of $SfvO_2$ and $ScvO_2$ were assessed, including the difference between $SfvO_2$ and $ScvO_2$.

Results Despite significant correlation between obtained values of $SfvO_2$ and $ScvO_2$ (r_s = 0.55; $p < 0.001$), the limits of agreement (LOA) were wide in the control group (mean bias 2.7% ± 7.9%; 95% LOA: -12.9 to 18.2%). In both the surgical and critically ill patients, LOA (mean bias of -1.9% ± 9.3%; 95% LOA: -20.0% to 16.3%, and mean bias of 4.6% ± 14.3%; 95% LOA: -23.5% to 32.6%, respectively) were wide. Results for changes of $SfvO_2$ and $ScvO_2$ were similar. During initial treatment of critically ill patients, the difference between $SfvO_2$ and $ScvO_2$, including its range of variation diminished.

Conclusion There is lack of agreement between $SfvO_2$ and $ScvO_2$ in both stable and unstable medical conditions. Thus, $SfvO_2$ should not be used as surrogate for $ScvO_2$.

Introduction

Shock is defined as global tissue hypoxia secondary to an imbalance between systemic oxygen delivery (DO_2) and oxygen demand (VO_2). Unrecognized and untreated global tissue hypoxia increases morbidity and mortality [1-3]. Measurement of mixed venous oxygen saturation (SvO_2) from the pulmonary artery (PA), i.e. the downstream site of the circulation, has been advocated as an indirect index of tissue oxygenation [4]. Hence, SvO_2 reflects the balance between oxygen delivery and demand [5]. The normal range for SvO_2 is 65 to 75% [4,6] and low SvO_2 is predictive of bad outcome [4,7]. However, PA catheterization is costly and obtaining the first SvO_2 values may be relatively time consuming. As a result of these disadvantages and an international debate on the use of PA catheter [8-10] its use has become, justifiable or not [11], somewhat unpopular.

Just as SvO_2, the measurement of central venous oxygen saturation ($ScvO_2$) has been described to detect global tissue hypoxia. Early goal-oriented manipulation of cardiac preload, afterload and contractility, to restore the balance between systemic oxygen delivery and oxygen demand has been shown to improve outcome [12]. Although there has been considerable debate on equality or interchangeability of $ScvO_2$ and SvO_2, $ScvO_2$ has been used as a therapeutic goal in resuscitation protocols as a surrogate marker for SvO_2 [13].

To monitor $ScvO_2$, insertion of a central venous catheter in the superior vena cava via the jugular or subclavian vein is required. However, sometimes the femoral vein is the preferred (inexperienced hands) or only possible (trauma; previous attempts failed) site for access in acutely ill patients. As shown in a recent survey, femoral catheters are commonly used during the first hours of treatment of critically ill patients [14]. Apart from possible disadvantages compared to jugular or subclavian portal such as arterial puncture and thrombosis [15], the use of femoral catheters has several advantages. Femoral access is quick, relatively safe and radiographic control is not required [16] because there is no risk for

pneumothorax. Hence, the femoral venous access can be very useful in the care of acutely ill patients.

There is little information on the relevance of $SfvO_2$ [14,17,18]. The purpose of our study is first to determine if $ScvO_2$ and femoral venous oxygen saturation ($SfvO_2$) can be used interchangeably in critically ill patients and in high-risk surgery and second, to evaluate whether changes in $SfvO_2$ may be used as a parameter for treatment.

Methods

Study centre

This prospective, observational, controlled study was performed in a non-academic university affiliated teaching hospital in The Netherlands [Gelre Hospital location Lukas in Apeldoorn, The Netherlands]. The ICU is a 12-bed “closed format” department. Per year about 17,500 surgical procedures are performed in this hospital. The study was approved by the Local Ethics Committee. Written informed consent was obtained in all cases from the patient or from the patient’s legal representative.

Patients and data collection

Three groups of patients were analyzed. First, 100 stable cardiac outpatients who underwent elective right heart catheterization in day care. This population served as control group. Second, 30 high-risk (ASA score > 2) patients who underwent elective intermediate / high-risk surgery (surgical patients). Third, 30 consecutive critically ill patients who were acutely admitted to the ICU either directly from the ED, from the general ward or after acute surgery with septic shock [19] or cardiogenic shock [20] (ICU patients).

All included patients were older than 18 years. Exclusion criteria were acute abdominal or thoracic aneurysm, pregnancy, lack of data (technical problems) or lack of written informed consent.

In the control group not only $ScvO_2$ and $SfvO_2$, but also SvO_2 was determined. During the right heart catheterizations 3 samples (femoral vein, proximal inferior caval vein, pulmonary artery) were obtained after routine cannulation of the femoral vein. Correct position of the catheter was confirmed by real-time angiography.

In the surgical patients samples were obtained simultaneously before start of the procedure, i.e. after induction but before application of sterile sheeting (T=0), and at the end of the procedure, i.e. after sterile sheeting was removed (T=1). In the ICU patients samples were simultaneously obtained in the first hour of resuscitation (T=0) as soon as the central venous line was in place, and 6 hours thereafter (T=1). Femoral blood samples were obtained by puncture.

In the surgical and ICU patients hemodynamic measurements as well as blood samples and arterial blood gas analyses were recorded. Also, the use of fluids, packed red blood cells and vasopressors were recorded.

Central venous catheters [Edwards Lifesciences LLC, Irvine, CA, USA; usable length 16 cm.] were inserted into an internal jugular vein or subclavian vein according to standard procedure. Correct position in the superior caval vein was confirmed by the presence of central venous pressure tracings and chest radiography. No complications other than transient arrhythmias were observed during the insertion of any catheter. In case of the use of a pulmonary artery catheter (PAC) [Criticath SP 5507H TD, Becton Dickinson, Singapore] in the ICU, blood samples were drawn from the proximal port of the catheter as representative of central venous blood [21-23]. All blood samples were analyzed by a co-oximeter (Radiometer ABL800 flex, Copenhagen, Denmark). The Acute Physiology, Age and Chronic Health Evaluation (APACHE) II-score was collected for ICU patients [24].

Statistical analysis

Statistical tests were two-tailed and performed by the statistical package for the social sciences (IBM SPSS 19 for Windows, Chicago, IL, USA). GraphPad software (Prism 5, version 5.02 for Windows, and StatMate 2.0, San Diego, CA, USA) was used for graphics. Measurements were not independent but clustered within each patient. All data were tested for normal distribution with the D'Agostino-Pearson omnibus normality test before further statistical analysis. T-test (paired) was used where appropriate. Non-parametric testing of continuous variables was performed using Mann-Whitney-U test or Wilcoxon's paired rank-sum test. Otherwise the Fisher's exact test was used. For both time points (T=0 and T=1) in the surgical and ICU group, ($SfvO_2$ - $ScvO_2$) was calculated.

Paired samples were compared by (Spearman, r_s) correlation [25] and the agreement between absolute values of $ScvO_2$ and $SfvO_2$ and the agreement of the changes of these values were assessed by the mean bias and 95% limits of agreement (mean bias ± 1.96 x standard deviation (SD)) as described by Bland and Altman (BA analysis) [26]. Limits of agreement (LOA) were considered acceptable if they were within 5%. Based on the findings in the control group (SD 7 to 10; r = 0.60) we determined that number of paired samples required for a 90% power in a two-sided test with a 0.05 type I error would be 30. Data are displayed as median [interquartile range (IQR)]. Statistical significance was assumed at $p < 0.05$.

Results

Control group

In 100 patients (46 males, 54 females) who underwent elective right heart catheterization we obtained 100 paired blood samples. Median age was 73 [63 - 80] years.

SvO_2 and $ScvO_2$ correlated significantly ($p < 0.001$) with $r_s = 0.85$. BA analysis revealed a bias (or absolute difference) of 0.5% ± 2.8% (95% LOA of -4.8 to 5.9%).

Median $SfvO_2$ was lower than median SvO_2 (66.3 [58.1 - 73.0]% vs. 68.9 [64.3 – 72.6]%; p=0.03). According to BA analysis the mean bias between SvO_2 and $SfvO_2$ was 2.1% ± 7.9%; 95% LOA -13.0 to 17.5%. Correlation between SvO_2 and $SfvO_2$ was significant ($r_s = 0.57$; $p < 0.001$).

Results for median $SfvO_2$ and median $ScvO_2$ were very similar. Median $SfvO_2$ was lower than $ScvO_2$ (66.3 [58.1 - 73.0]% vs. 69.2 [64.9 - 73.2]%; $p < 0.01$) According to BA analysis the bias between $ScvO_2$ and $SfvO_2$ was 2.7% ± 7.9% 95% LOA were -12.9 to 18.2% (figure 1). Fifty-five percent of the paired $SfvO_2$ and $ScvO_2$ samples diverged by > 5%. Nevertheless, $ScvO_2$ correlated with $SfvO_2$ ($r_s = 0.55$; $p < 0.001$).

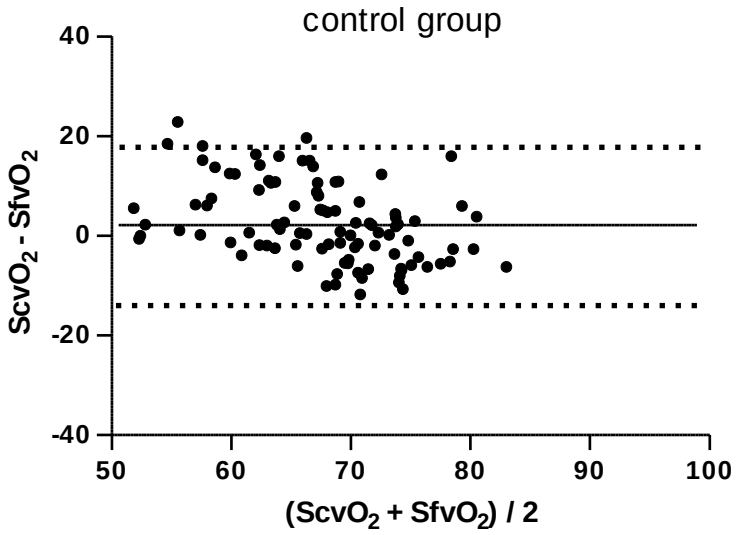

Figure 1. Control Group. Bland and Altman plot showing the agreement between $ScvO_2$ and $SfvO_2$ (bias 2.7%, 95% LOA from -12.9% to 18.2%).

Surgery group

Altogether 60 paired blood samples were obtained in 30 patients. Baseline characteristics are shown in table 1. Co-morbidities in this group of surgical patients: arterial hypertension (20), cardiac (atrial fibrillation, coronary artery disease) (12), diabetes mellitus (9), chronic obstructive pulmonary disease (6), neurological (6), other (21).

Table 1. Characteristics of surgical and ICU patients

variable	surgery (n=30)	ICU (n=30)	P value	septic shock (n=26)
age (yr)	75 [64 - 81]	75 [67- 80]	0.98	75 [67 - 82]
gender (male / female)	15 / 15	19 / 11	0.43	15/11
MAP (mmHg)	74 [66 - 81]	74 [63 - 90]	0.75	74 [61 - 90]
heart rate (beats / minute)	73 [62 - 87]	109 [96 - 131]	< 0.001	107 [96 - 114]
hematocrit (%)	30.0 [27.8 - 34.0]	33.5 [30.0 - 37.0]	0.05	32.0 [30.0 - 35.5]
FiO_2	0.45 [0.40 - 0.50]	0.60 [0.40 - 0.65]	0.10	0.58 [0.40 - 0.60]
APACHE II		22 [17- 28]		24 [15 - 30]
CVC (jugular / subclavian)	29 / 1	14 / 16	<0.001	12 / 14
$ScvO_2$ (%)	81.0 [78.0 - 86.5]	77.0 [65.8 - 83.3]	0.02	78.0 [65.7 - 83.0]
$SfvO_2$ (%)	83.0 [78.0 - 88.0]	71.0 [58.8 - 82.0]	< 0.001	74.0 [63.5 - 81.2]

ICU, intensive care unit; MAP, mean arterial pressure; FiO_2, fraction of inspired oxygen; APACHE II, acute physiology, age and chronic health evaluation; CVC, central venous catheter; $ScvO_2$, central venous oxygen saturation; $SfvO_2$, femoral venous oxygen saturation. Data are presented as median [IQR] or as numbers; P value, ICU vs. surgery.

Types of surgery (and number) performed on these patients were as follows: liver (9), lung (8), colon (6), aorta (4), and other (3). Median length of stay in the hospital (LOS_{HOSP}) was 10 [6-19] days. Post-operative complications included: pneumonia (4), ileus (4), relaparotomy (4), cardiac ischemia (3), de novo atrial fibrillation (2), neurological (1), wound infection (1), urinary tract infection (1), systemic inflammatory response syndrome (1), pulmonary embolus (1), and other (5). None of the patients died postoperatively in the hospital.

At T=0 the $SfvO_2$ underestimated the $ScvO_2$ (bias of -1.9% ± 9.3%). The 95% LOA were -20.0% to 16.3% (figure 2). At T=1 the $SfvO_2$ underestimated the $ScvO_2$ (bias of -1.0% ± 14.9%). The 95% LOA ranged from -30.2% to 28.3% (figure 2). At both time points $SfvO_2$ and $ScvO_2$ did not correlate significantly ($p = 0.23$ and $p = 0.06$, respectively). The differences between median ($SfvO_2$ - $ScvO_2$) at T=0 and T=1 were not significant (2.0 [-5.0 - 7.5]% vs. 4.0 [-6.5 - 7.0]%; $p = 0.71$). The median changes of $SfvO_2$ and $ScvO_2$ from T = 0 to T = 1 were equivalent (-5.0 [-13.8 - 5.8]% vs. -2.0 [-11.0 - 2.5]%; $p = 0.89$). In only 57% the changes in $SfvO_2$ and $ScvO_2$ over time were in the same direction; this was independent of the type of surgery.

ICU group

Thirty acutely admitted patients were included. Baseline characteristics are shown in table 1. At admission, four patients were in cardiogenic shock based on acute coronary syndrome or cardiac failure. Twenty-six patients were in septic shock. Causes of sepsis were respiratory (n=13), abdominal (n=8), urological (n=2), or other (n=3). In the majority of patients (28/30) one or more inotropes were used (28/30): dopamine (n=1), norepinephrine (n=16), milrinone (n=26), isoprenaline (n=1).

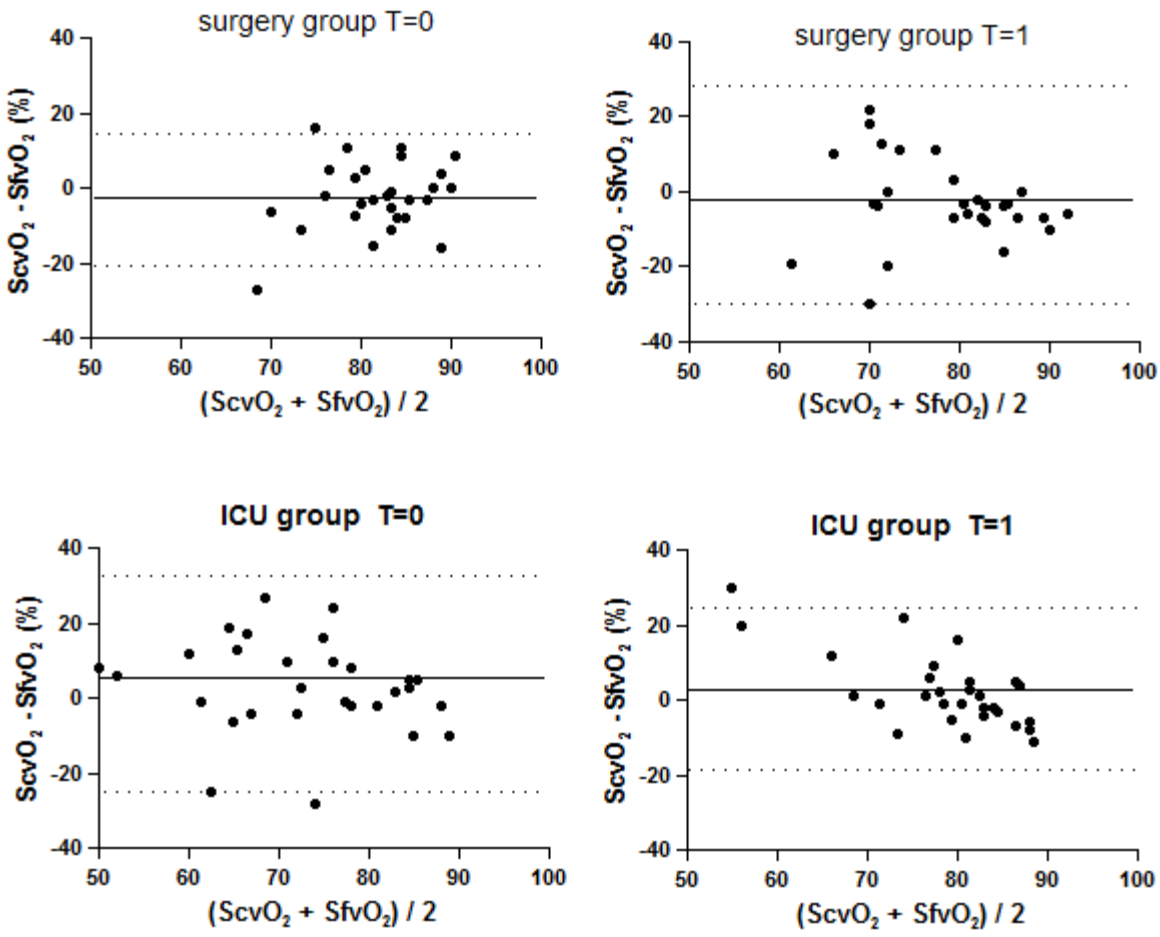

Figure 2. Bland and Altman plots showing the agreement between $ScvO_2$ and $SfvO_2$ in the surgery group at T=0 and T=1 and in the ICU group at T=0 and T=1; various bias and 95% LOA in results section.

At T=0 the $SfvO_2$ overestimated the $ScvO_2$ (bias of 4.6% ± 14.3%). The 95% LOA were -23.5% to 32.6% (figure 2). At T=1 the $SfvO_2$ overestimated the $ScvO_2$ (bias of 3.3% ± 11.1%). The 95% LOA ranged from -18.5% to 25.1% (figure 2). At both time points $SfvO_2$ and $ScvO_2$ correlated significantly (p = 0.01 and p = 0.002, respectively) with comparable r_s (0.46 vs. 0.55). The difference between $SfvO_2$ and $ScvO_2$ and the range of variation diminished over time (from -4.0 [range -44.0 to 28.0] at T=0 to -1.0 [range -32.0 to 11.0] at T=1; figure 3).

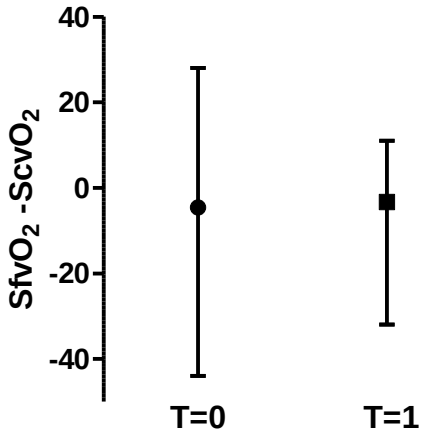

Figure 3. ICU group. The median difference between $SfvO_2$ and $ScvO_2$ at T=0 (-4.0%, range -44% to 28%) and T=1 (-1.0%, range -32% to 11%).

Changes of $SfvO_2$ and $ScvO_2$ over time occurred in the same direction in 87% of the cases (26/30; in-hospital mortality 27% (7/26)). In twenty of these patients the value of both $SfvO_2$ and $ScvO_2$ increased; mortality of this subgroup was 25% (5/20). In four cases $ScvO_2$ increased after treatment while $SfvO_2$ decreased. In-hospital mortality in this small subgroup (75% (3/4)) was not significantly higher compared to the other 26 patients (p=0.33). The 95% LOA between both changes were -32.6% to 30.1%. The total in-hospital mortality in this group was 33%.

Results for 26 patients in septic shock were similar to the results of the total ICU group (table 1). At T=0 the $SfvO_2$ overestimated the $ScvO_2$ (bias of 2.2% ± 12.8%). The 95% LOA were -27.5% to 22.8%. At T=1 the $SfvO_2$ overestimated the $ScvO_2$ (bias of 3.5% ± 11.9%). The 95% LOA ranged from -26.5% to 19.9%. At both time points $SfvO_2$ and $ScvO_2$ correlated significantly (p = 0.01 and p = 0.003, respectively) with comparable r_s (0.43 vs. 0.54). Median LOS_{HOSP} was 13 [5-27] days and in-hospital mortality was 35% (9/26).

Comparison between patient groups

Gender and age were equally distributed in the control and surgery group (table 2). The absolute values of $SfvO_2$ and $ScvO_2$ were higher in the surgery group compared to the control group (table 2). The difference between $SfvO_2$ and $ScvO_2$ values also varied significantly between study groups (table 2).

Table 2. Comparison of study groups (T=0)

	control (n = 100)	surgery (n=30)	P value [a]	ICU (n=30)	P value [b]
age (year)	73 [63-80]	75 [64 - 81]	0.39	75 [67-80]	0.41
gender (m / f)	46 / 54	15 / 15	0.83	19 / 11	0.14
$ScvO_2$ (%)	69.2 [64.9 - 73.2]	81.0 [78.0 - 86.5]	<0.001	77.0 [65.8 - 83.3]	<0.001
$SfvO_2$ (%)	66.3 [58.1 - 73.0]	83.0 [78.0 - 88.0]	<0.001	71.0 [58.8 - 82.0]	0.06
$SfvO_2$ - $ScvO_2$ (%)	-1.5 [-8.5 - 2.7]	2.0 [-5.0 - 7.5]	0.03	-4.0 [-12.3 - 2.5]	0.37

ICU, intensive care unit; m, male; f, female; $ScvO_2$, central venous oxygen saturation; $SfvO_2$, femoral venous oxygen saturation; $SfvO_2$ - $ScvO_2$, difference between $SfvO_2$ and $ScvO_2$; [a] surgery vs. control group; [b] ICU vs. control group; Data are presented as median [IQR] or as numbers.

In contrast to the median value of $SfvO_2$ median value of $ScvO_2$ was higher in the acutely admitted critically ill patients compared to the patients in the control group.

The absolute values of the venous oxygen saturations were significantly lower in the septic ICU patients ($ScvO_2$ 77.0 [65.8 - 83.3]%; $SfvO_2$ 71.0 [58.8 - 82.0]%) than in surgical patients ($ScvO_2$ 81.0 [78.0 - 86.5]%; $SfvO_2$ 83.0 [78.0 - 88.0]%) at T=0. This difference disappeared at T=1 (table 3).

Table 3. Characteristics surgical and ICU patients at different time points

variable	surgery (n=30)	ICU (n=30)	P value
T = 0			
MAP (mmHg)	74 [66 - 81]	74 [63 - 90]	0.75
heart rate (beats / minute)	73 [62 - 87]	109 [96 - 131]	< 0.001
$ScvO_2$ (%)	81.0 [78.0 - 86.5]	77.0 [65.8 - 83.3]	0.02
$SfvO_2$ (%)	83.0 [78.0 - 88.0]	71.0 [58.8 - 82.0]	< 0.001
FiO_2	0.45 [0.40 - 0.50]	0.60 [0.40 - 0.65]	0.10
$SfvO_2$ - $ScvO_2$	2.0 [-5.0 - 7.5]	-4.0 [-12.3 - 2.5]	0.03
T = 1			
MAP (mmHg)	77 [72 - 94]	65 [59 - 74]	< 0.001
heart rate (beats / minute)	82 [66 - 99]	99 [84 - 109]	0.03
$ScvO_2$ (%)	79.0 [72.8 - 83.0]	81.5 [75.0 - 83.3]	0.47
$SfvO_2$ (%)	83.0 [71.5 - 87.0]	79.5 [72.0 - 85.0]	0.46
FiO_2	0.45 [0.40 - 0.67]	0.45 [0.40 - 0.60]	0.53
$SfvO_2$ - $ScvO_2$	4.0 [-6.5 - 7.0]	-1.0 [-6.8 - 4.3]	0.08
change of $ScvO_2$ ($T_1 – T_0$)	-2.0 [-11.0 - 2.5]	5.0 [1.0 - 10.3]	0.001
change of $SfvO_2$ ($T_1 – T_0$)	-5.0 [-13.8 - 5.8]	4.5 [-4.8 - 21.0]	0.01
total infusion (ml)	3150 [1534 - 4795]	3286 [2369 - 5135]	0.43
fluid balance (ml)	272 [-525 - 1127]	2589 [1137 - 3721]	0.01

ICU, intensive care unit; MAP, mean arterial pressure; FiO_2, fraction of inspired oxygen; APACHE II, acute physiology, age and chronic health evaluation; CVC, central venous catheter; $ScvO_2$, central venous oxygen saturation; $SfvO_2$, femoral venous oxygen saturation. Data are presented as median [IQR] or as numbers.

Discussion

We conclude that $SfvO_2$ should not be used as a surrogate of $ScvO_2$ due to the lack of agreement between both variables under different circumstances. This uncertainty in estimating $ScvO_2$ by $SfvO_2$ hampers protocol-guided hemodynamic optimization in which decreases in $SfvO_2$ of $ScvO_2$ may trigger therapeutic interventions. As for the absolute values of $SfvO_2$ and $ScvO_2$, substituting the change of $ScvO_2$ by the change of $SfvO_2$ is not suitable. These results are of confirmative but also additional value with respect to recent reports on populations of critically ill patients [14, 17].

This is the first study describing the relationship between femoral and non-femoral central venous saturations in outpatients. Although those patients do not resemble healthy volunteers, the results will give us at least an idea of the physiological relationship between femoral and non-femoral central venous saturations in stable hemodynamic conditions. In these stable conditions without any reason for redistribution of blood flow, the median values of $ScvO_2$ or SvO_2 and $SfvO_2$ were significantly different, and LOA as described by BA analysis were wide. Apparently, even in stable hemodynamic conditions a statement on the systemic balance between oxygen delivery and oxygen demand should not be based on $SfvO_2$ values.

No study compared $ScvO_2$ and $SfvO_2$ in surgical patients before. In the present study mean biases between $ScvO_2$ and $SfvO_2$ were relatively small during anesthesia in intermediate and high-risk surgery but LOA were wide. The Bland and Altman projections implacably demonstrate that several values differed even more than 15% from each other. Even more concerning was the lack of predictability for the direction of change of $ScvO_2$ by $SfvO_2$: it's like tossing a coin. We think that peri-operative protocols as suggested for $ScvO_2$ [27,28] should not be based on $SfvO_2$ values.

Treatment of shock implies improvement of the circulatory state with redistribution of flow not only in vital organs but also in more peripheral tissue, including limbs. The results in the ICU group elegantly show that after 6 hours of intensive treatment the mean difference between $SfvO_2$ and $ScvO_2$ decreased, i.e. after reversal of shock and improvement of the circulation $SfvO_2$ approached $ScvO_2$. In the vast majority of patients changes of $SfvO_2$ and $ScvO_2$ occurred in the same direction, i.e. rise or fall, during resuscitation. Although not significant due to insufficient power, the mortality rate was higher when $ScvO_2$ increased but $SfvO_2$ decreased after 6 hours of treatment in the ICU (3/4; 75%). Apparently, in these cases treatment failed to improve circulation and shock was not adequately reversed. Also, regional (splanchnic, leg blood flow) changes in oxygen delivery and consumption cannot predict systemic changes [28] and differences in regional oxygen extraction ratio [29] attribute to the differences between $ScvO_2$ and $SfvO_2$ in our study. In conclusion, $SfvO_2$ did not adequately predict $ScvO_2$ in critically ill patients. This is in line with recent clinical work in which a similar lack of agreement between $SfvO_2$ and $ScvO_2$ was described [14,17]. Both studies describe wide LOA as well, i.e. more than 50% of $ScvO_2$ and $SfvO_2$ values diverged by more than 5% [14,17]. Although in those studies more critically ill patients (n=39 and n=43, respectively) were included than in the present study, our study carries a control group and compares changes of both values over time.

Several strengths of this study should be mentioned. First, a relatively large group of stable cardiac patients served as control group. Second, a power analysis was performed before the start of the study. Third, we did not only compare absolute values but also changes over time of both $ScvO_2$ and $SfvO_2$ during treatment in surgery and in the ICU. Fourth, femoral blood samples were taken by puncture, which excludes possible influences of the catheter length on oxygen content or reliability of the samples.

However, this study also has limitations. First, measurements were done intermittently and not continuously. Second, all surgical and ICU patients were sedated, mechanically ventilated, and none of them were primarily in hemorrhagic shock. Therefore care must be taken before generalizing our results to other patients with different pathophysiology. Third, we investigated acutely admitted ICU patients and timing of measurements was probably not always in the same stage of disease. However, this approach reflects common clinical practice and is a well-known drawback in all studies involving critically ill patients. Fourth, one may argue that movements of the legs, especially during global hypoxia may have influenced the results. However, all cardiac patients were stable, locally anaesthetized and lying still during the procedure. All surgical and most (28 out of 30) ICU patients were measured after induction of general anesthesia. The other two ICU patients were quiescent at the time of measurements. Furthermore, the occurrence of strong leg movements would have caused even larger differences between $ScvO_2$ and femoral venous saturations than reported in our results. Hence, we do not think this potential confounder plays a role in our study. Finally, in this study $ScvO_2$ and $SfvO_2$ values did not change between different time points as a result of a study intervention. However, measurements took place within individual patients: each subject served as its own control.

Conclusion

$SfvO_2$ cannot replace $ScvO_2$, neither in stable conditions nor during surgery or during the resuscitation phase in critically ill patients.

References

1. Rady MY, Rivers EP, Novak RM: **Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate**. *Am J Emerg Med* 1996; **14**: 218-225.
2. Wo CC, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E: **Unreliability of bloodpressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness.** *Critical Care Medicine* 1993; **21**: 218-223.
3. Vincent JL, De Backer D: **Oxygen uptake/oxygen supply dependency: fact or fiction?** *Acta Anaesthesiol Scand Suppl* 1995; **107**: 229-237.
4. Kandel G, Aberman A: **A Mixed venous oxygen saturation: its role in the assessment of the critically ill patient.** *Arch Int Med* 1983; **143**: 1400-1402.
5. Reinhart K, Schäfer M, Rudolph T: **Mixed venous oxygen saturation**. *Appl Cardiopulm Pathophysiol* 1989; **2**: 315-325.
6. Nelson LD: **Continuous venous oximetry in surgical patients**. *Ann Surg* 1986; **203**: 329-333.
7. Kasnitz P, Druger Gl, Yorra F, Simmons DH: **Mixed venous oxygen tension and hyperlactataemia. Survival in severe cardiopulmonary disease**. *JAMA* 1976; **236**: 570-574.
8. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell Jr FE, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson Jr WJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA: **The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT investigators**. *JAMA* 1996; **276**: 889-897.
9. Sakr Y, Vincent JL, Reinhart K, Payen D, Wiedermann CJ, Zandstra DF, Sprung CL: **Use of the pulmonary catheter is not associated with worse outcome in the ICU**. *Chest* 2005; **128**: 2722-2731.
10. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, Brampton W, Williams D, Young D, Rowan K: **Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial.** *Lancet* 2005; **366**: 472-477.

11. Vincent JL: **So we use less pulmonary artery catheters – But why?** *Crit Care Med* 2011; **39**: 1820-1822.

12. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; for the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock**. *N Engl J Med* 2001; **345**: 1368-1377.

13. van Beest PA, Wietasch JKG, Scheeren TWL, Spronk PE, Kuiper MA: **Clinical review: use of venous oxygen saturations as a goal – a yet unfinished puzzle**. *Crit Care* 2011; **15**: 232.

14. Davison DL, Chawla LS, Selassie L, Jones EM, McHone KC, Vota AR, Junker C, Sateri S, Seneff MG: **Femoral-based central venous oxygen saturation is not a reliable substitute for subclavian/internal jugular-based central venous oxygen saturation in patients who are critically ill.** *Chest* 2010; **138**: 76-83.

15. Marino PL: **The ICU book**, 3rd ed, Philidelphia, Lippincot Williams & Wilkins, 2007.

16. Swanson RS, Uhlig PN, Gross PL, McCabe CJ: **Emergency intravenous access through the femoral vein**. Ann Emerg Med 1984; **13**: 244-247.

17. Groombridge CJ, Duplooy D, Adams BD, Paul E, Butte W: **Comparison of central venous pressure and venous oxygen saturation from venous catheters placed in the superior vena cava or via a femoral vein: the numbers are not interchangeable**. *Crit Care Resusc* 2011; **13**: 151-155.

18. Regli A, De Keulenaer BL, Hockings LE, Musk GC, Roberts B, van Heerden PV: **The role of femoral venous pressure and femoral venous oxygen saturation in the setting of intra-abdominal hyperetension: a pig model**. *Shock* 2011; 35: 422-427.

19. Levy MM, Fink MP, Mashall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; **International Sepsis Definitions Conference: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference.** *Intensive Care Med* 2003; **29**: 530-538.

20. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K: **ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008**. *Eur Heart J* 2008; **29**: 2388-2442.

21. Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M: **Lack of equivalance between central and mixed venous oxygen saturation**. *Chest* 2004; **126**: 1891-1896.

22. van Beest PA, van Ingen J, Boerma EC, Holamn ND, Groen H, Koopmans M, Spronk PE, Kuiper MA: **No agreement of mixed venous and central venous saturation in sepsis, independent of sepsis origin**. *Crit Care* 2010; **14**: R219.

23. Gutierrez G, Comignanni P, Huespe L, Hurtado FJ, Dubin A, Jha V, Arzani Y, Lazzeri S, Sosa L, Riva J, Kohn W, Suarez D, Lacuesta G, Olmos D, Mizdraji C, Ojeda A: **Central venous to mixed venous blood oxygen and lactate gradients are associated with outcome in critically ill patients**. *Intensive Care Med* 2008; **34**: 1662-1668.

24. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system**. *Crit Care Med* 1985; **13**: 818-829.

25. Edwards AL: **An introduction to lineair regression and correlation**. 2nd ed. New York, NY: WII Freeman 1984: 70-76.

26. Bland JM, Altman DG: **Agreement between methods of measurement with multiple observations per individual**. *J Biopharm Stat* 2007; **17**: 571-582.

27. Shepherd SJ, Pearse RM: **Role of central and mixed venous oxygen saturation measurement in perioperative care**. *Anesthesiology* 2009; **111**: 649-656.

28. Donati A, Loggi S, Preiser JC, Orsetti G, Münch C, Gabbanelli V, Pelaia P, Pietropaoli P: **Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients**. *Chest* 2007; **132**: 1817-1824.

29. Sander M, Spies CD, Foer A, Weymann L, Braun J, Volk T, Grubitzsch H, von Heymann C: **Agreement of central venous oxygen saturation and mixed venous oxygen saturation in cardiac surgery patients**. *Intensive Care Med* 2007; **33**: 1719-17-25.

Chapter 5

Measurement of lactate in a prehospital setting is related to outcome

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Abstract

Objective We evaluated the relationship of lactate measured in a pre-clinical setting to outcome. Simultaneously, we evaluated the feasibility of implementing blood lactate measurement in a pre-hospital setting as part of a quality improvement project.

Methods Chart review of patients from whom serum lactate levels prospectively were obtained in a pre-hospital setting. Total population was divided into two groups, i.e. a shock group and a non-shock group according to predefined shock symptoms. The shock group was divided into two groups, i.e. a lactate < 4mmol/L (subgroup I) and a lactate ≥ 4mmol/L (subgroup II).

Results In about 50% of possible cases lactate was measured in the pre-hospital setting. Median lactate in subgroup I (n=74) was 3.2 (1.5-3.9) mmol/L vs. 5.0 (4.0-20.0) mmol / L in subgroup II (n=61) ($p < 0.0001$). Significant differences were found in length of stay in intensive care unit ($p = 0.03$) or hospital ($p = 0.04$) and mortality (subgroup I 12.2% vs. subgroup II 44.3%; $p = 0.002$). In normotensive shock patients revealing a lactate ≥ 4mmol/L (n=27) the mortality was higher compared to normotensive shock patients with a lactate < 4mmol/L (n=31) (35% vs. 7%; $p < 0.001$).

Conclusion Implementation of lactate measurement in pre-hospital setting is feasible, and potentially clinical relevant. Lactate measured in a pre-clinical setting is related to outcome. Subsequent studies should evaluate if treatment of shock patients based on pre-hospital lactate measurement will improve outcome.

Introduction

Physical findings and vital signs are important, but not always sufficient for accurate detection of global tissue hypoxia [1]. Global tissue hypoxia as a result from systemic inflammatory response or circulatory failure is an important indicator of shock preceding multiple organ dysfunction syndrome (MODS). Due to global tissue hypoxia, with concomitant risk of developing an oxygen debt, anaerobic metabolism occurs and lactate production is increased. If this situation persists, the lactate metabolic clearance rate is surpassed and circulating lactate levels may be elevated as well.

Numerous studies have established the use of lactate as a diagnostic, therapeutic and prognostic marker in different shock states and other critical conditions [2-5]. Serum lactate concentrations > 4 mmol/L are unusual in normal and not critically ill hospitalized patients, independent of underlying comorbidities [6]. Lactate concentration > 4 mmol/L in the presence of systemic inflammatory response syndrome (SIRS) criteria significantly increases intensive care unit (ICU) admission rates and mortality rate in normotensive patients [7]. Also, lactate represents a useful and clinically obtainable surrogate marker of tissue hypoxia and disease severity, independent of blood pressure [8]. This was corroborated by others, who also demonstrated that early lactate clearance was associated with decreased mortality rate in patients with severe sepsis and post-cardiac arrest patients [9,10]. These findings have facilitated the clinical application of point-of-care measurements and portable monitoring of lactate over the past decade in the emergency department (ED), operating theatre and ICU [11-13]. In addition, several years ago Shapiro et al. suggested that lactate seemed a promising risk-stratification tool in the ED setting [14]. They found a significant higher mortality rate in patients with a serum lactate ≥ 4 mmol/L. Measurement of serum lactate in a pre-hospital setting, i.e. in the ambulance, could warn paramedics of pending organ failure despite normal global hemodynamic parameters. We evaluated the relationship of lactate measured in a pre clinical setting to outcome. Simultaneously, we evaluated the

feasibility of implementing blood lactate measurement in a pre-hospital setting as part of a quality improvement project.

Methods

Setting

We studied charts of ambulances that arrived at a non-academic medical centre [Gelre Hospital (GH), site Lukas, Apeldoorn, The Netherlands]. These charts are standardized by the Dutch ambulance organization. The GH is an affiliated 925-bed teaching hospital and the ICU is a 14-bed “closed format” department. The ambulance service covers an area of about 2000 km^2 with approximately 620,000 inhabitants. The ambulance service is divided into 4 clusters, the main cluster being Apeldoorn, an urban area with approximately 270,000 inhabitants.

Implementation

From an environmental scan [15] we learned that in the Netherlands measurement of lactate has not been done in daily practice throughout the pre-hospital phase. Because lactate measurement was an unknown feature for our ambulance personnel the next phase of implementation, setting a target, seemed important to prepare them for a change in behaviour. To make behavioural change possible, teaching regarding *why*, *what*, and *when* for changing behaviour is crucial. During the two months prior to the first blood lactate measurements in pre-hospital setting all ambulance personnel was trained. First, as part of the education program, one of the investigators (PS) explained in a lecture the theoretical essence of this project. The *why*, the expected potential benefit for shock patients in the future was also mentioned. Finally, all ambulance personnel received a two hour course on working with the lactate meter (Accutrend© lactate meter (Roche Diagnostic GmbH) in the

field. This course was not only theoretical but also contained actual practice. With this course we intended to lower the threshold in the field for the use of an extra device. The emphasis on *who* to change was focused on the ambulance personnel.

Patients and data collection

This study is a chart review of patients from whom serum lactate levels prospectively were obtained in a pre-hospital setting. Total population was divided into two groups, i.e. a shock group and a non-shock group according to predefined shock symptoms which were defined as 1) a heart rate <50 or >100 beats per minute, 2) systolic blood pressure <90 mmHg, 3) respiration rate <10 or >30 breaths per minute, 4) peripheral arterial oxygen saturation <95% (COPD patients <90%), 5) collapse or Glasgow Coma Scale (GCS) <14. Patients suffering from two or more of these symptoms were included in the shock group; those with none or one deviated shock parameter were included in the control (non-shock) group. Exclusion criteria were age <18 years, hypoglycemia, seizures, no consent, treatment not according to the Dutch national ambulance protocol ("Landelijk Protocol Ambulance", LPA 7) or lacking data. In the field respiration rate was noted according to the Dutch national ambulance chart, being five options: none, 1-5, 6-9, 10-29 and more than 30 breaths per minute. For analysis, respiratory rates were divided into three categories: 0-9, 10-29 and >30 breaths per minute [16]. After defining the non-shock and shock group the latter population was divided into two subgroups: one subgroup with blood lactate < 4 mmol/L (= subgroup I) and another subgroup with blood lactate ≥ 4 mmol/L (= subgroup II). Early treatment given in pre-hospital setting was divided in three categories: 1) oxygen plus basic peripheral IV line; 2) as previous, plus plasma expander; 3) as previous, plus intubation.

Lactate measurements

During the maintenance phase all lactate meters (Accutrend© lactate meter (Roche Diagnostic GmbH) were calibrated regularly according instructions by the manufacturer. Capillary or venous lactate levels were measured with these meters. Local coordinators were interviewed on the experiences of the ambulance personnel, the lactate meter and its use in the field. Also points for improvement were noted.

Vitals were determined with Lifepack© 12 (Medtronic). Collecting data was approved by the Medical Ethics Committee. Informed consent was obtained from all participants.

Statistical analysis

The statistical package for the social sciences (SPSS 16.0.1 for Windows) was used for statistical analysis. All data were tested for normal distribution with the Kolmogorov-Smirnov test before further statistical analysis. Since normality could not be assumed, differences between groups were assessed using non-parametric Mann-Witney U analysis and Spearman correlation tests. Data were displayed as median and range. Categorical data were tested by χ^2 test. Receiver operating curves (ROC) curves were used to describe the relation between increased lactate levels and vital signs and to evaluate their reliability as a prognostic factor. In all cases a p-value < 0.05 was considered to be statistical significant.

Results

Implementation

In about 50% of possible cases lactate was measured in the pre-hospital setting in the Apeldoorn area. The number of measurements was lower in more rural areas (24%). Interviews with coordinators in the 4 clusters of the ambulance service revealed consistently the same causes of non-compliance and the following barriers were encountered. Duration of lactate measurement (60 seconds) resulted in restraint for a successive attempt. In the rural areas especially, less frequent calls resulted in less experience in handling the lactate meter. Measurement seemed less aggravating for ambulance personnel when for instance patients hemodynamics were less deteriorated or when GCS was high or normal. Although personnel were well aware of the possible reasons *why* to change medical acting in the field variation from standard protocol (LPA 7) was still an issue. Overall, the majority of ambulance personnel experienced inclusion criteria as too strict. An extra measurement was not always considered possible in sometimes-stressful situations. On the other hand, occasional feedback on particular cases such as repeated lactate measurements in the ED or ICU was experienced as positive.

Lactate measurements

As a result of the implementation of lactate measurement in the pre-hospital setting a total 277 ambulance charts were reviewed, allowing evaluation of clinical relevance. Sixty-one charts did not meet inclusion criteria: forty-one patients were in pre-hospital setting diagnosed with seizures, eighteen charts were invalid and two patients were not treated according to the national ambulance protocol leaving 216 charts fit for study. Eighty-one

patients did not meet shock criteria (non-shock group) but 135 patients did (shock group). Characteristics of the patients are shown in table 1.

The numbers of shock criteria per patient in the shock group were distributed as follows: 2 criteria in 55 (40.8%) patients; 3 criteria in 41 (30.6%) patients; 4 criteria in 28 (20.4%) patients and 5 criteria in 11 (8.1%) patients. In normotensive shock patients (MAP 60-90mmHg) revealing a lactate ≥ 4mmol/L (n=27) the mortality was higher compared to normotensive shock patients with a lactate < 4mmol/L (n=31) (35% vs. 7%; $p < 0.001$). Median lactate in the shock group was significantly higher compared to the non-shock group: 3.9 (1.5-20.0) mmol/L vs. 2.8 (0.8-7.2) mmol/L ($p < 0.0001$). In hospital mortality differed significantly from the non-shock group: 26.7% in the shock group vs. 1.2% in the control group ($p < 0.001$).

In the shock subgroups (subgroup I: lactate < 4 mmol/L, n=74; subgroup II: lactate ≥ 4 mmol/L, n=61) age and sexes were equally distributed. Median lactate in subgroup I was 3.2 (1.5-3.9) mmol/L vs. 5.0 (4.0-20.0) mmol / L in subgroup II ($p < 0.0001$). Compared to subgroup I more patients showed an unfavourable respiratory pattern in subgroup II (category respiratory rate <10 or >29 breaths / minute) (35.1%vs. 65.6%). Only one patient (1.4%) needed intubation in subgroup I but 15 patients (24.6%) needed intubation in subgroup II ($p < 0.001$). Also significant differences were found in length of stay in intensive care unit or critical care unit (LOS_{ICU}) ($p = 0.03$), length of hospital stay (LOS_{HOSP}) ($p = 0.04$) and mortality (subgroup I 12.2% vs. subgroup II 44.3%; $p = 0.002$). Results within the shock group are shown in table 2.

Table 1. Base-line characteristics of non-shock and shock group.

	non-shock group (n=81)	shock group (n=135)	P value
Age (yr)	54 (18-94)	72 (18-91)	< 0.001*
Sex (%)			
Male	56.8	60.0	0.67
Female	43.2	40.0	
Heart rate (beats per minute)	75 (51-146)	91 (0-150)	0.005*
Mean blood pressure (mmHg)	97 (61-133)	73 (0-140)	<0.0001*
Respiratory rate			0.004*
0-9	0	14	
10-29	76	69	
>29	5	52	
Arterial saturation (%)	98 (84-100)	92 (0-100)	<0.0001*
Lactate (mmol/L)	2.8 (0.8-7.2)	3.9 (1.5-20.0)	<0.0001*
GCS	15 (6-15)	14 (3-15)	<0.0001*
RTS	12 (10-12)	11 (0-12)	<0.0001*
Diagnosis (%)			
Trauma	9.9	5.9	
Respiratory failure	1.2	8.9	
Cardiac failure (incl. resuscitation)	1.2	14.1	
Sepsis / infection	1.2	14.1	
Haemorrhage	7.4	18.5	
Acute abdomen	16.0	8.1	
CNS	2.5	6.7	
Other	60.6	23.7	
$LOS_{ICU/CCU}$ (days)	0 (0-1)	1 (0-46)	<0.0001*
LOS_{HOSP} (days)	1 (0-26)	4 (0-53)	<0.0001*
In hospital mortality (%)	1.2	26.7	<0.0001*

Data presented as numbers or median (range). * Statistically significant difference. GCS, Glasgow Coma Scale; RTS, Revised Trauma Score; CNS, central nervous system; $LOS_{ICU/CCU}$, length of stay in intensive or critical care unit; LOS_{HOSP}, length of stay in hospital.

Receiver operating characteristic (ROC) curves were constructed for measurements taken in pre-hospital setting. These curves represent the reliability of different values as predictors of in-hospital mortality. Area under the curve (AUC) was significantly higher for lactate compared to vitals in both the total population (lactate 0.827 vs. SaO_2 0.127, MAP 0.350 and heart rate 0.500; $p < 0.01$) and the shock group (lactate 0.775 vs. SaO_2 0.157, MAP 0.421 and heart rate 0.435; $p < 0.01$). We established a lactate level of 3.2mmol/L as the best cut-off point. A lactate level of ≥ 3.2mmol/L was 75% sensitive (95% CI 62-88%) and 72% specific (62-82%) for prediction of death; figure 1.

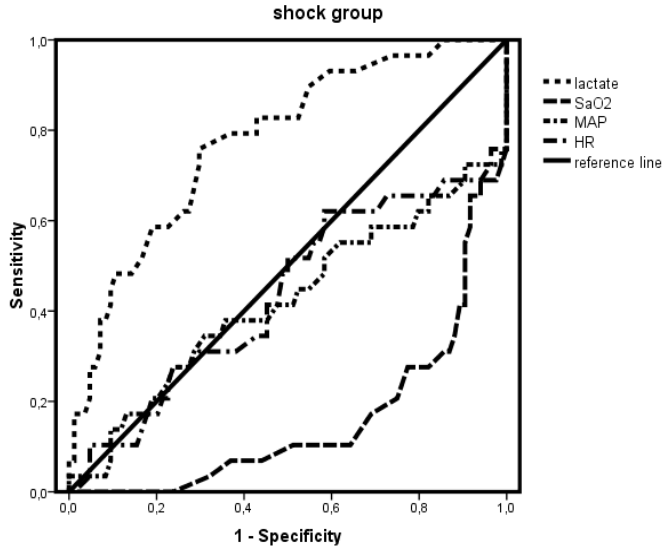

Figure 1. ROC curves for mortality prediction in the shock group. The AUC was 0.775 for lactate, 0.157 for arterial saturation (SaO_2), 0.421 for mean arterial pressure (MAP) and 0.435 for heart rate (HR).

Table 2. Base-line characteristics subgroups of shock patients.

	subgroup I (n=74) (lactate < 4 mmol/L)	subgroup II (n=61) (lactate ≥4 mmol/L)	p-value
Age (yr)	74 (18-90)	70 (19-91)	0.59
Sex (%)			
Male	56.8	63.9	0.40
Female	43.2	36.1	
Heart rate (beats per minute)	82 (35-150)	99 (0-140)	0.20
Mean blood pressure (mmHg)	78 (34-140)	70 (0-140)	0.77
Respiratory rate			0.01*
0-9	3	11	
10-29	48	21	
>29	23	29	
Arterial saturation (%)	94 (47-100)	88 (0-100)	< 0.0001*
Lactate (mmol/L)	3.2 (1.5-3.9)	5.0 (4.0-20.0)	< 0.0001*
GCS	15 (3-15)	15 (3-15)	0.68
RTS	11 (5-12)	10 (0-12)	0.01*
Diagnosis (%)			0.07
Trauma	4.1	8.2	
Respiratory failure	12.2	4.9	
Cardiac failure (incl. resuscitation)	9.5	19.7	
Sepsis / infection	10.8	18.0	
Haemorrhage	14.9	23.0	
Acute abdomen	10.8	4.9	
CNS	6.8	6.6	
Other	30.9	14.7	
$LOS_{ICU/CCU}$ (days)	0 (0-12)	1 (0-46)	0.03*
LOS_{HOSP} (days)	1 (0-53)	7 (0-46)	0.04*
In hospital mortality (%)	12.2	44.3	0.02*

Data presented as numbers or median (range). * Statistically significant difference. GCS, Glasgow Coma Scale; RTS, Revised Trauma Score; CNS, central nervous system; $LOS_{ICU/CCU}$, length of stay in intensive or critical care unit; LOS_{HOSP}, length of stay in hospital.

Discussion

Logistical implementation of lactate measurement on the ambulance services means implementation of an extra medical act and extra effort. We concluded that this is feasible, albeit difficult. One of the reasons for this difficulty is that we aimed at changing behaviour without the presence of logistical or procedural errors that often motivate clinical collectives to action [15]. Also, involving ED personnel, including consultants may enhance the chance of success in a complex and dynamic environment such as the acute care that only can function as result of interplay of diverse departments and teams [15,17]. Difficulty with lactate measurements in very stressful situations or even ignoring such measurement during these events seems reasonable. Lactate measurements are probably less important in patients being resuscitated and in need for instant and maximum treatment. In these cases the urgency is obvious and will be carried over to the ED personnel. However, during the interviews it became clear that for the ambulance personnel lactate measurement in patients with less deteriorated hemodynamics seemed less necessary. This is a pity, for lactate measurement in the pre-hospital setting could especially be of use in this category of patients: i.e. patients being more severely ill than could suspected by vitals only. Consequently, a substantial number of patients with prognostically important hypoperfusion remain undetected. Most importantly, high lactate levels should trigger for specific intervention, i.e. fluid therapy, to improve lactate clearance and to improve outcome[18]. Treatment aiming at high lactate clearance is associated with decreased mortality rate in severe sepsis patients with elevated baseline lactate but without hypotension [9]. Our results seem concordant with the latter finding, i.e. mortality was significantly increased in normotensive shock patients if their pre-hospital lactate level was ≥ 4mmol/L (7% vs. 35%). Again, this finding is important because those patients would probably not be identified as being critically ill in the pre-hospital or ED setting. Recently Howell et al. also found higher mortality rates with increased lactate levels (≥4 mmol/L) in normotensive patients. In their patient population with suspected infection they confirmed that a single lactate measurement

was independently predictive of mortality and not a surrogate marker of hypotension [19]. Early lactate determination seems helpful for triage decisions, not only in the ED, but also before ED presentation. Patients might indeed benefit from advanced activation of medical staff in the destination hospital.

Several limitations to our observations should be mentioned. First, this quality improvement project was not powered to yield conclusions pertaining to the obtained lactate measurements. Nevertheless, the data are interesting, since even in this small study strong association between lactate and increased morbidity and mortality could be demonstrated. This illustrates the importance of measuring lactate in the pre-hospital setting. Still, lactate measurements were not compared with the lactate levels in the ED. Consequently, the influence of lactate clearance could not be described and the use of the threshold value of 3.2mmol/L may therefore be of limited value. Second, lactate was measured either from venous or capillary blood. Lactate determination in an ED or ICU can be done form venous or arterial blood sample and in most previous studies on lactate measurements were done arterially. In pre-hospital setting this is however not possible and venous (capillary) samples are the first choice. Previous studies showed these measurements to be equivalent [20,21]. Finally, the lactate measurements are predominantly performed in the Apeldoorn area and thus reflect a single centre observation. Further studies should reveal whether successful implementation in several ambulance regions may yield comparable results and if lactate measurements in the pre-hospital setting could be used as guideline for treatment.

We conclude that implementation of lactate measurement in pre-hospital setting is feasible, albeit difficult and potentially clinical relevant. Subsequent studies should evaluate if treatment based on pre-hospital lactate measurement will improve outcome.

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References

1. Rady MY, Rivers EP, Novak RM: **Resuscitation of the critically ill in the ED. responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate.** *Am J Emerg Med* 1996; **14**: 218-225.
2. Moomey CB Jr, Melton SM, Croce MA, Fabian TC, Proctor KG: **Prognostic value of blood lactate, base deficit, and oxygen-divided variables in an LD50 model of penetrating trauma.** *Crit Care Med* 1999; **27**: 154-161.
3. Bakker J, Coffernils M, Leon M, Gris Ph, Vincent JL: **Blood lactate levels are superior to oxygen-divided variables in predicting outcome in human septic shock.** *Chest* 1991; **99**: 956-962.
4. Henning RJ, Weil MH, Weiner F: **Blood lactate as a prognostic indicator of survival in patients with acute myocardial infarction**. *Circ Shock* 1982; **9**: 307-315.
5. Blow O, Magliore L, Claridge JA, Butler KRN, Young JS. **The golden hour and the silver day: detection and correction of occult hypoperfusion within 24 hours improves outcome from major trauma**. *J Trauma* 1999; **47(5)**: 964-976.
6. Kruse JA, Zaidi SA, Carlson RW. **Significance of blood lactate levels in critically ill patients with liver disease.** *Am J Med* 1987; **83**: 77-82.
7. Aduen J, Bernstein WK, Khastgir T, Miller J, Kerzner R, Bhatiani A et al. **The use and clinical importance of a substrate-specific electrode for rapid determination of blood lactate concentrations.** *JAMA* 1994; **272**: 1678-1685.
8. Bernardin G, Pradier C, Tiger F, Deloffre P, Mattei M. **Blood pressure and arterial lactate levels are early indicators of short-term survival in human septic shock.** *Intensive Care Med* 1996; **22**: 17-25.
9. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC: **Early ,lactate clearance is associated with improved outcome in severe sepsis and septic shock**. *Crit Care Med* 2004; **32**: 1637-1642.
10. Donnino MW, Miller J, Goyal N, Loomba M, Sanskey SS, Dolcourt B, Sherwin R, Otero R, Wira C: **Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients**. *Resuscitation* 2006; **75**: 229-234.

11. Steinfelder-Visscher J, Weerwind W, Teerenstra S, Brouwer MHJ: **Reliability of point-of-care hematorcrit, bloodgas, electrolyte, lactate and glucose measurement during cardiopulmonary bypass**. *Perfusion* 2006; **21**: 33-37.

12. Asimos AW, Gibbs MA, Marx JA, Jacobs DG, Erwin RJ, Norton HJ, Thomason M: **Value of point-of-care blood testing in emergent trauma management**. *J Trauma* 2000; **48(6)**: 1101-1108.

13. Boldt J, Kumle B, Suttner S, Haisch G: **Point-of-care (POC) testing of lactate in the intensive care patient**. *Acta Anaesthesiol Scan* 2001; **45**: 194-199.

14. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, Weiss JW: **Serum lactate as a predictor of mortality in emergency department patients with infection**. *Ann Emerg Med* 2005; **45 (5)**: 524-528.

15. Cook DJ, Montori VM, McMullin JP, Finfer SR, Rocker GM: **Improving patients' safety locally: changing clinician behaviour**. *The Lancet* 2004; **363**: 1224-1230.

16. Buist MD, Moore GE, Bernard SE, Waxman BP, Anderson JN, Nguyen HB: **Effects of an emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study**. *BMJ* 2002; **324**: 387-390.

17. Bradley EH, Holmboe ES, Mattera JA, Roumanis SA, Radford MJ, Krumholz HM: **A qualitive study of increasing β-blocker use after myocardial infarction: why do some hospitals succeed?** *JAMA* 2001; **285**: 2604-2611.

18. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; for the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**: 1368-1377.

19. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI: **Occult hypoperfusion and mortality in patients with suspected infection.** *Intensive Care Med* 2007; **33(11)**: 1892-1899.

20. Lavery RF, Livingston DH, Tortella BJ, Sambol JT, Slomovitz BM, Siegel JH: **The utility of venous lactate to triage injured patients in the trauma center**. *J Am Coll Surg* 2000; **190(6)**: 656-664.

21. Weil MH, Michaels S, Rackow EC: **Comparison of blood lactate concentrations in central venous, pulmonary artery, and arterial blood**. *Crit Care Med* 1987; **15(5)**: 489-490.

Chapter 6

Cumulative lactate in ICU patients: magnitude matters

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Abstract

Objective To evaluate whether lactate levels and derived variables are associated with organ failure and in-hospital mortality in a mixed intensive care unit (ICU) population.

Methods Retrospective observational study. Case records from 2251 consecutive ICU patients admitted between 2001 and 2007 were analyzed. Base line characteristics, all lactate measurements, Sequential Organ Failure Assessment (SOFA) scores and in-hospital mortality were recorded. The time integral of arterial blood lactate levels above the upper normal threshold of 2.2 mmol/L (lactate-time-integral), maximum lactate (max-lactate), and time-to-first-normalization, were calculated. Survivors and non-survivors were compared and receiver operating characteristic (ROC) analysis were applied.

Results A total of 20755 serum lactate measurements were analyzed. In non-survivors (n=405) lactate-time-integral, time-to-normal and cumulative SOFA were higher than in hospital survivors (all $p<0.001$). AUC of ROC curves to predict in-hospital mortality was the largest for max-lactate, whereas it was not different among all other lactate derived variables (all $p>0.05$). The area under the ROC curves for admission lactate and lactate-time-integral was not different ($p=0.36$).

Conclusion Cumulative lactate is associated with in-hospital mortality in a heterogeneous ICU population. In our patients lactate peak values, but not the time integral of arterial blood lactate levels above the upper normal threshold predicted in-hospital mortality.

Introduction

Hyperlactataemia is common in critically ill patients and may reflect an imbalance between local or systemic oxygen supply (DO_2) and oxygen consumption (VO_2). Hyperlactataemia may also be found during increased aerobic glycolysis in hypermetabolic states from various causes [1,2], in patients treated with catecholamines [3,4], as a consequence of alkalosis in hyperventilation [5], and with impaired hepatic lactate clearance in sepsis or low flow states [6]. Elevated serum lactate levels are associated with the development of multiple organ dysfunction (MODS) postoperatively, following trauma, and septic shock [7-10] and it has been suggested that hyperlactataemia is associated with worse outcome [10-13]. Persistence of lactate levels above normal is associated with higher mortality rates in patients with severe sepsis, septic shock [9,14] and in post-cardiac arrest patients [15]. We hypothesized that the duration of hyperlactataemia represented by the time integral of arterial blood lactate levels above the upper normal threshold of 2.2 mmol/L (lactate-time-integral) outperforms single lactate measurements in predicting outcome.

We therefore retrospectively investigated the relationship between lactate derived variables (admission level, maximum level, time-to first-normalization, lactate-time-integral) and organ failure, as assessed by the Sequential Organ Failure Assessment (SOFA) score [16-18], as well as in-hospital mortality in a large, mixed ICU population. Additionally, we performed subgroup analysis on categories in which lactate has been described as predictor of mortality (sepsis and circulatory failure) [10-13].

Methods

Setting

A retrospective observational study in a university affiliated teaching hospital where the ICU is a mixed, 10 bed “closed format” department. There were no changes in medical staff during the study period. Case records from all ICU patients with available serum lactate measurements admitted over a 5-year period, January 2002 - December 2006, were identified in the ICU database. The study was approved by the Local Ethics Committee that waived the need for informed consent.

Data collection

Data from all days spent in the ICU were collected retrospectively from the electronic patient data monitoring system and the hospital administration database. We collected demographic information, diagnosis, acute physiology and chronic health evaluation (APACHE II), simplified acute physiology score (SAPS-II), all serum lactate levels, and relevant variables for calculation of daily-assessed SOFA score (table 1). Diagnosis classifications were based on the APACHE II classifications, hence diagnosis category weight [19]. Finally, length of stay in the ICU (ICU_{LOS}), days in the hospital before discharge (LOS_{HOSP}) and hospital survival were recorded.

Parameters of organ failure

SOFA scores were prospectively calculated daily during ICU stay on a routine basis. The highest value for each organ system in the preceding 24-hour period was used. If variables required for calculation were missing, they were considered as normal until the first

measured value became available. For any missing value thereafter, the last measured value known was used. The following SOFA-derived variables were used:

1. Initial SOFA score on the first day of ICU admission (from time of admission to 24 hours following admission, e.g., from 6 am to 6 am the next day).
2. Cumulative SOFA (cum-SOFA): the sum of all daily SOFA scores during the stay in the ICU.

If the patient received renal placement therapy (RRT) the maximum of 4 points was used for the renal component of the SOFA score.

Lactate levels and derived variables

Lactate levels were measured in arterial blood using point-of-care blood gas analyzers (Rapidlab 865, Siemens, Munich, Germany; upper normal limit 2.2mmol/L).

The time integral for lactate levels above the upper normal threshold of 2.2 mmol/L was calculated during the entire ICU-stay (lactate-time-integral) using custom made software. We used a formula that, for practical reasons, assumed a linear change over time between measurements. Figure 1 illustrates four possible scenarios used for calculating lactate-time-integral. Lactate buffer solutions for RRT and continuous epinephrine infusion were not used during the study period following the general policy in the unit.

Statistical analysis

The statistical package for the social sciences (SPSS 16.0.1 for Windows, Chicago, IL, USA) was used for statistical analyses and additional software was used for graphics (Prism 5.0 for windows, La Jolla, CA, USA) and comparison of ROC curves (MedCalc 11.2.1, Mariakerke, Belgium). Data are presented as mean ± SD or

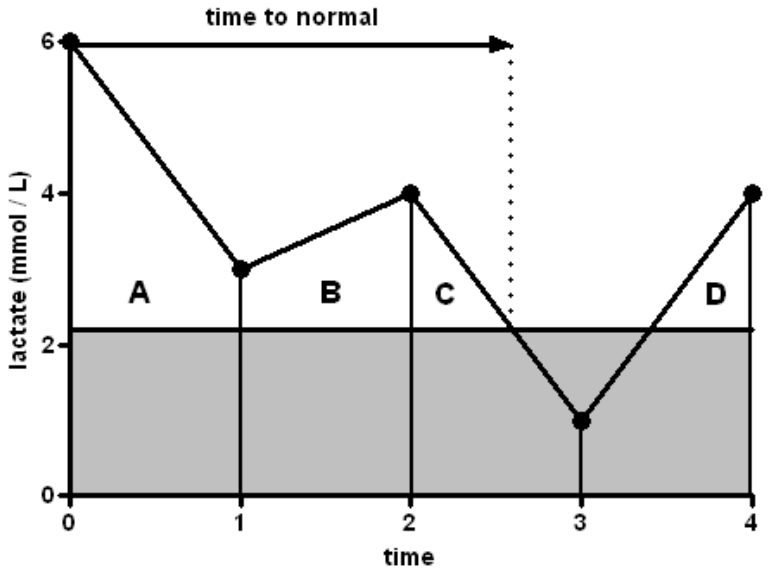

Figure 1. Illustration on calculation of lactate area under the curve above the upper normal limit of serum lactate (2.2 mmol/L). The following four equations were used in computing lactate-AUC:

1. AUC A = ((½ · (lactate 0 – lactate 1)) + lactate 1)) · (time 1 – time 0)
2. AUC B = ((½ · (lactate 2 – lactate 1)) + lactate 1)) · (time 2 – time 1)
3. AUC C = ((lactate 2 – 2.2)² · (time 3 – time 2)) / 2 · lactate 2
4. AUC D = ((lactate 4 – 2.2)² · (time 4 – time 3)) / 2 · lactate 4

median [inter-quartile range] as indicated by assessment of normal distribution (D'Agostino-Pearson omnibus normality test). Wilcoxon rank-sum test was used for categorical data. Differences of admission source or admission diagnosis between groups of survivors and non-survivors and those with and without hyperlactataemia were assessed using the Chi square test. Receiver Operating Characteristic (ROC) curves were used for the assessment of sensitivity and specificity of lactate derived variables in predicting in-hospital mortality. Areas under the ROC curves (AUC_{ROC}) were compared by the method described by DeLong et al. [20]. Statistical significance was assumed at $p < 0.05$.

Results

Table 1. Baseline and clinical characteristics

characteristics	all n = 2251	surv n = 1846	non surv n = 405	P value [a]
age (yr)	66 (12-98)	69 (57-76)	75 (67-81)	
sex M : F (%)	61 : 39	61 : 39	60 : 40	
SAPS-II	38 (20-113)	33 (24-43)	51 (41-65)	< 0.001 [*]
APACHE II	17 (10-54)	15 (11-19)	23 (17-28)	< 0.001 [*]
diagnosis (%)				< 0.01 [#*]
vasc surg	16.0	17.2	10.4	
abd surg	22.4	23.5	17.2	
other surg	9.8	10.9	4.9	
heart failure	14.8	12.3	26.4	
resp failure	11.8	11.5	13.4	
GI bleeding	3.8	4.3	1.5	
neurological	4.5	4.6	2.7	
other	3.7	3.9	4.2	
sepsis	13.1	11.8	19.2	
vasoactive agent (%)	33	28	57	< 0.001 [*]
LOS ICU (days)	2 (1-5)	2 (1-5)	3 (1-8)	< 0.001 [*]
LOS HOSP (days)	14 (7-27)	15 (9-28)	6 (2-16)	< 0.001 [*]
in hosp mortality (%)	18			

Data are presented as numbers and median (interquartile range). AUC, area under the curve; surv, survivors; non surv, non-survivors; SAPS-II, simplified acute physiology score; APACHE II, acute physiology, age and chronic health evaluation; vasc surg, vascular surgery; abd surg, abdominal surgery; resp failure, respiratory failure; GI, gastrointestinal; vasoactive agent: noradrenaline, dopamine, dobutamine, phosphodeisterase inhibitor; LOS ICU, length of stay at intensive care; LOS HOSP, length of stay at hospital; in hosp mortality, in-hospital mortality; [a] survivors vs. non-survivors, [*] Statistically significant difference. Statistics by Chi-square tests [#] and Wilcoxon rank-sum tests.

During the 5-year period case records of 2251 patients (age 66 [12-98] years; 39% female) were identified. A total of 20755 serum lactate measurements were analyzed. Median lactate concentration at admission was 1.7 [1.1-2.8] mmol/L; minimum 0.6 mmol/L and maximum 27.0 mmol/L. Max-lactate was 2.1 [1.5-3.3] mmol/L, and lactate-time-integral 0.0 [0.0-244] min·mmol/L. Baseline and clinical characteristics of all patients are summarized in table 1 (total population) and table 2 (subgroups).

Table 2. Baseline characteristics subgroups

characteristic	**sepsis n=307**	**respiratory failure n=303**	**cardiac failure n=213**	**trauma n=76**	**hemorrhage n=165**
age (yr)	69 (60-77)	68 (57-76)	72 (63-78)	37 (24-66)	70 (58-78)
sex M : F (%)	63 : 37	58 : 42	60 : 40	75 : 25	61 : 38
SAPS II	48 (37-57)	39 (31-50)	48 (37-63)	24 (17-35)	36 (28-45)
APACHE II	21 (17-26)	18 (14-22)	22 (16-28)	11 (8-16)	15 (11-19)
heart rate (beats/min)	115 (96-130)	115 (95-130)	110 (80-125)	95 (80-110)	100 (85-115)
syst BP (mmHg)	105 (80-130)	123 (105-140)	110 (85-140)	123 (105-140)	105 (85-135)
MAP (mmHg)	58 (50-62)	63 (55-69)	59 (51-65)	65 (58-74)	62 (55-70)
vasoactive agent (%)	56	36	56	20	31
mech. ventilation (%)	49	47	63	59	36
lactate (mmol/L)	2.4 (1.6-3.9)	1.7 (1.1-2.6)	2.4 (1.4-4.8)	2.0 (1.4-3.2)	1.0 (0-2.1)
max lactate (mmol/L)	3.0 (2.1-4.9)	2.1 (1.6-2.9)	3.0 (1.9-5.2)	2.3 (1.5-3.3)	1.2 (0-2.8)
cum-lactate (min·mmol/L)	216 (0-2634)	0 (0-143)	138 (0-1245)	1 (0-243)	0 (0-38)
in hosp mortality (%)	29	21	38	8	8

Data are presented as numbers and median (interquartile range). SAPS-II, simplified acute physiology score; APACHE II, acute physiology, age and chronic health evaluation

In-hospital mortality of our population was 18% and was higher in patients with hyperlactataemia during ICU-stay compared to those without hyperlactataemia (26.4% vs. 10.8%; p < 0.001; table 1). In patients who died in the hospital (n = 405), admission lactate (2.6 [1.5-5.0] mmol/L), max-lactate (3.2 [1.9-5.8] mmol/L) and lactate-time-integral (192 [0-1881] min·mmol/L), were higher than in hospital survivors (n = 1846; admission lactate (1.6 [1.1-2.5] mmol/L), max-lactate (2.0 [1.4-3.0] mmol/L) and lactate-time-integral 0 [0-134] min·mmol/L, respectively; all p < 0.001); Figure 2.

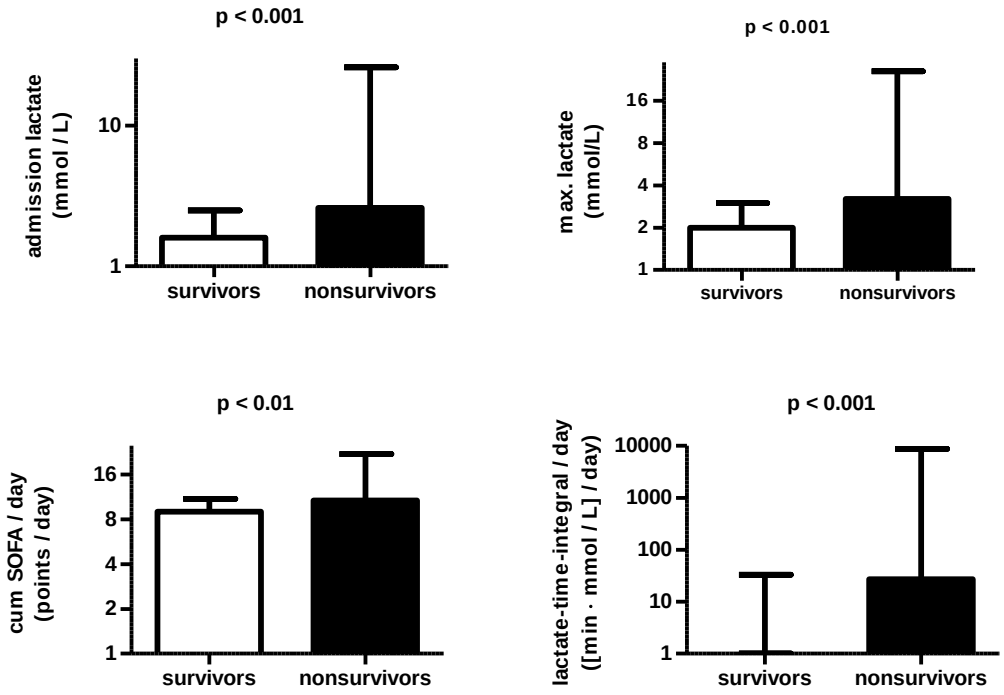

Figure 2. Admission lactate levels (mmol/L), maximum lactate levels (mmol/L), cum-SOFA per day (points/day), lactate-time-integral per day ([min·mmol/L]/day) for survivors (n = 1846) and non-survivors (n = 405); bars show median (upper interquartile range); logarithmic scale.

Figure 3 illustrates the relationship between lactate-time-integral per day and cum-SOFA per day in survivors (n=1846) and non-survivors (n=405). Geometric means [95% CI] of lactate-time-integral per day ([min·mmol/L] / day) and of cum-SOFA per day (points / day) were significantly higher in non-survivors (174 [128-236] min·mmol/L / day and 11.1 [10.5-11.8] points / day) compared to survivors (44 [40-51] min·mmol/L / day and 9.1 [8.9-9.4] points / day); both $p < 0.001$.

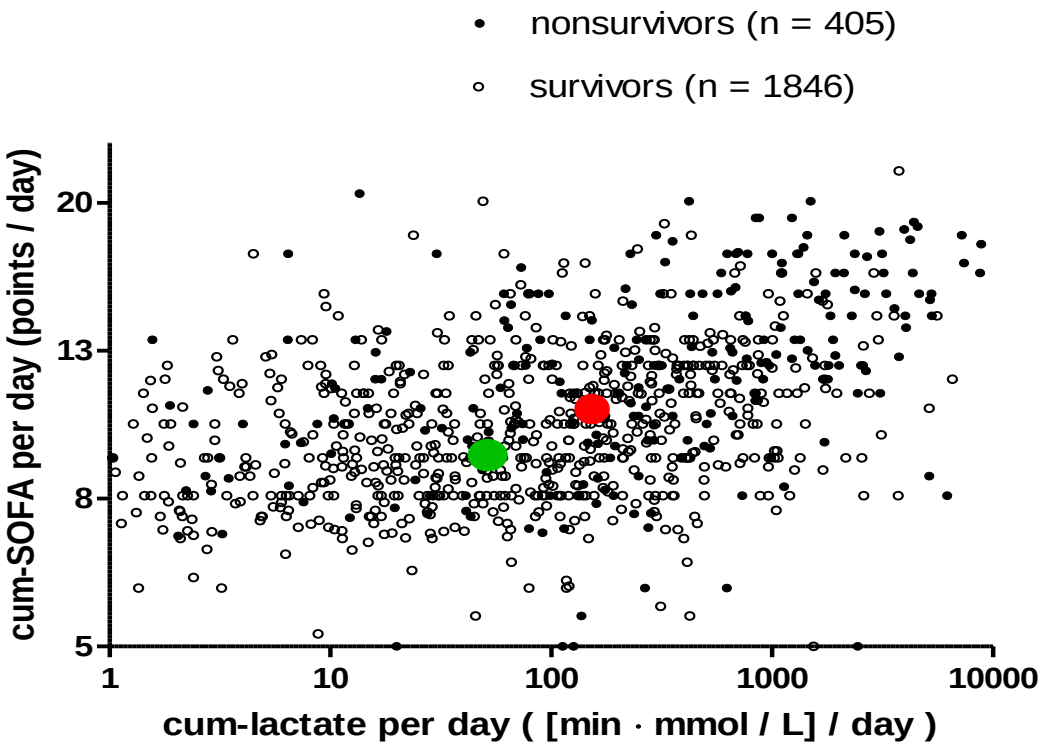

Figure 3. Relationship between lactate-time-integral per day and cum-SOFA per day in both survivors and non-survivors: geometric means (open dot: survivors, closed dot: non-survivors) with 95% confidence intervals; logarithmic scale.

Figure 4 demonstrates the difference between admission lactate levels and lactate-derived variables with respect to predicting in-hospital mortality. AUC_{ROC} for admission lactate and lactate-time-integral were similar (0.666 [95% CI 0.646 to 0.686] vs. 0.676 [95% CI 0.657 to 0.696]; p=0.36). AUC_{ROC} for max-lactate (0.692 [95% CI 0.672 to 0.711]) was

larger than AUC_{ROC} for lactate (0.666 [95% CI 0.646 to 0.686]; p = 0.01) lactate-time-integral (0.676 [95% CI 0.657 to 0.696]; p < 0.01), and time to normal (0.552 [95% CI 0.531 to 0.573]; p < 0.001). The cut-off points derived from the ROC curve for lactate, max-lactate and cumulative lactate were 2.7 mmol/L, 2.5 mmol/L and 53 min·mmol/L, respectively.

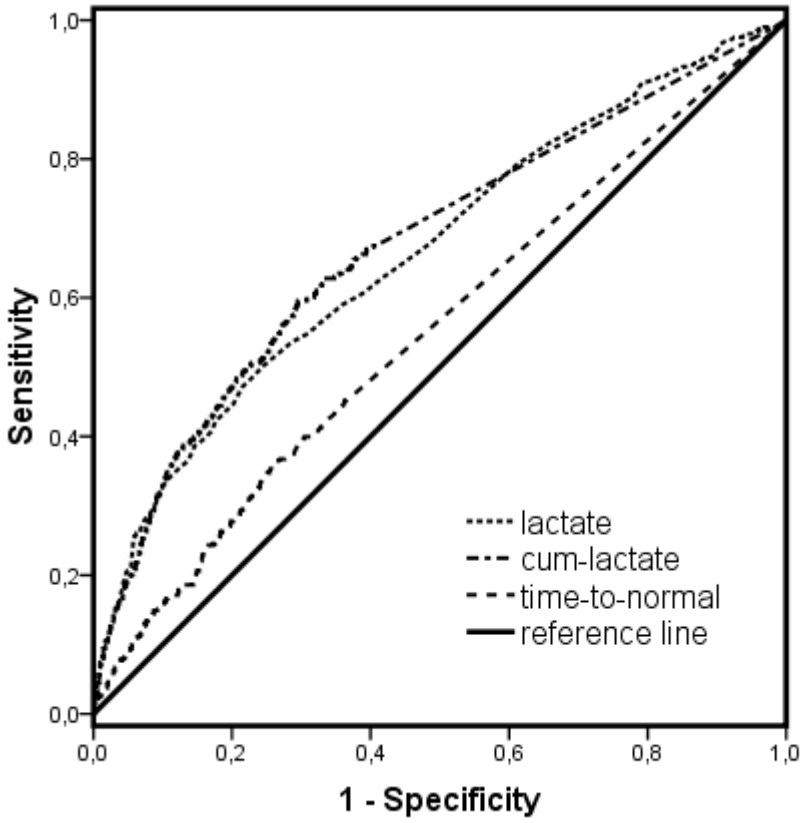

Fig. 4 Receiver operating characteristic curves for in-hospital mortality prediction. Area under the curve was 0.552 for time to normal, 0.666 for lactate, 0.676 for lactate-time-integral and 0.692 maximum lactate

Subgroup analysis revealed similar results. In none of the subgroups (sepsis, n=307; cardiac failure, n=213) AUC_{ROC} for lactate-time-integral was larger than AUC_{ROC} for single lactate values. In all subgroups admission lactate and maximum lactate differed between survivors and non survivors (all p < 0.001).

Discussion

In the present study lactate-time-integral was not superior in predicting in-hospital mortality compared to admission or maximum arterial lactate concentrations. Admission lactate values, maximum lactate values during ICU stay, and lactate-time-integral, were all associated with in-hospital mortality.

High lactate clearance within the first 6 hours of sepsis is associated with decreased 60-day mortality, even in the absence of arterial hypotension: survivors compared with non-survivors had a lactate clearance of 38 vs. 12%, respectively [14]. Recently, in a randomized study, the use of lactate clearance was described as an efficacious alternative for $ScvO_2$ (target > 70%) guided resuscitation of patients in septic shock [21]. However, due to practical reasons a treatment bias could not be excluded. Also, difference in protocol actions were small: despite a well performed study chance may have influenced the results. In the present study we did not look at lactate clearance as described by Nguyen et al, a ratio of lactate values, but a combination of the lactate derived variables used may be considered as a surrogate. Yet, in the subgroup of patients with sepsis the lactate-time-integral or time to normal did not outperform max-lactate. This was the case in a study in which the duration of hyperlactataemia, lactime, was the best discriminant of survival when the patients who died in the first 24 hours were excluded [10]. We performed a retrospective study and choose not to exclude those patients who died early after onset of the disease to picture the influence of lactate and lactate derived variables in clinical reality. In conclusion, the present results recognize the importance of lactate clearance as described by others but also underline the importance of magnitude of lactate values during ICU treatment.

A serum lactate threshold of ≥ 4 mmol/L has been used to initiate protocol-based resuscitation [22,23]. Such an approach might imply acceptance of intermediate serum lactate levels in the range of 2 to 4 mmol/L. However, elevated mortality rates are also described in critically ill patients with only moderate elevated serum lactate levels during or

even before admission to the emergency department (ED) [24-26]. Additionally, in two recent retrospective studies the relationship between lactate levels, lactate derived variables and outcome in critically ill patients was assessed. It was concluded that not only hyperlactataemia but also relative hyperlactataemia, i.e. lactate levels in the upper normal range, are associated with increased mortality [27,28]. Our results in ICU patients are concordant with these results and we believe that normal values provide a reasonable clinical sign that tissue oxygenation is adequate and the metabolism is primarily aerobic. Nevertheless, it is possible that a higher lactate concentration threshold would have revealed different results. In addition, our results suggest that presence of hyperlactataemia outperforms its persistence in predicting in-hospital mortality. This might also be explained by two other factors. First, the retrospective design of our study and the lack of a specific intervention protocol limits the generalisation of our results. Second, arterial lactate concentrations not only depend on lactate production but also on its clearance. It is not known whether one mechanism is more important than the other with respect to outcome prediction. Nevertheless, the mechanism causing hyperlactataemia may play an important role in outcome prediction, rather than the hyperlactataemia itself. For instance, as described in two recent reports [30,31], the severity of hyperlactataemia due to metformin accumulation alone does not predict outcome but even in those cases the causative role is uncertain. Also, co morbidities such as renal insufficiency of liver failure may play an additional role [30,31].

Finally, non-survivors revealed shorter LOS_{ICU} and LOS_{HOSP}, whereas lactate-time-integral was significantly higher in non-survivors compared to survivors. This means that non-survivors accumulate enough SOFA points to predict outcome independent of LOS_{ICU} as illustrated in figure 3. The duration and magnitude of increased serum lactate levels, represented by the area under the lactate curve, is associated with final outcome. Nevertheless, in the present study the specificity and sensitivity, described by AUC_{ROC}, of admission lactate and lactate-time-integral were similar in predicting in-hospital mortality.

Several limitations to our observations should be considered. First, this was a retrospective study, which precludes definitive conclusions. On top of that, there was no predefined lactate measurement or lactate-based goal-directed protocol. However, we consider the results strong enough to warrant further prospective studies analyzing the described phenomena, particularly, because the data were collected over a 5 year period and derived from a large group of patients. Second, this was a single unit study and therefore the results may only reflect the regional population and ICU management strategies. Nevertheless, we believe that selection bias was minimized since all consecutive admissions were included in the data analysis, since there was no change in medical staffing, and admission and discharge criteria were stable during the study period. Third, we assumed a linear change in time between two lactate measurements, which is a simplification of a real biologic process. However, we believe that our approach represents an approximation with acceptable precision for the purpose of the present study.

We conclude that lactate load correlated with cumulative SOFA score and is associated with in-hospital mortality in a heterogeneous ICU population. Additionally, magnitude of serum lactate levels and not necessarily duration of elevated serum lactate levels are of value in predicting in-hospital mortality.

References

1. Gutierrez G, Wulf ME: **Lactic acidosis in sepsis: a commentary**. *Intensive Care Med* 1996, **22**: 6-16.
2. Mizock BA: **Redox repairs, tissue hypoxia, organ dysfunction, and mortality**. *Crit Care Med* 2000, **28**: 270-272.
3. Day NPJ, Phu NH, Bethell DP, Mai NTH, Chau TTH, White NJ: **The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection.** *Lancet* 1996, **348**: 219-223.
4. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, Nabet P, Larcan A: **Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study**. *Intensive Care Med* 1997, **23**: 282-287.
5. Druml W, Grimm G, Laggner AN, Lenz K Schneeweiβ B: **Lactic acid kinetics in respiratory alkalosis**. *Crit Care Med* 1991, **19**: 1120-1124.
6. Levraut J, Ciebiera J-P, Chave S, Rabary O, Jambou P, Carles M, Grimaud D: **Mild hyperlactataemia in stable septic patients is due to impaired lactate clearance rather than overproduction**. *Am J Respir Crit Care Med* 1998, **157**: 1021-1028.
7. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry Sm, Greenspan J: **Lactate clearance and survival following injury.** *J Trauma* 1993, **35**: 584-589.
8. Donati A, Cornacchini O, Loggi S, Caporelli S, Conti G, Falcetta S, Alò F, Pagliariccio G, Bruni E, Preiser JC, Pelaia P: **A comparison among portal lactate, intramucosal sigmoid Ph, and delta CO2 (PaCO2 – regional Pco2) as indices of complications in patients undergoing abdominal aortic aneurysm surgery.** *Anesth Analg* 2004, **99**: 1024-1031.
9. Callaway DW, Shapiro NI, Donnino MW, Baker C, Rosen CL: **Serum lactate and base deficit as predictors of mortality in normotensive elderly blunt trauma patients.** *J Trauma* 2009, **66**: 1040-1044.
10. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. **Serial blood lactate levels can predict the development of multiple organ failure following septic shock**. *Am J Surg* 1996, **171**: 221-226.

11. Tuchschmidt J, Fried J, Swinney R, Sharma OMP: **Early hemodynamic correlates with survival in patients with septic shock**. *Crit Care Med* 1989, **17**: 719-723.

12. Weil MH, Afifi AA: **Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock).** *Circulation* 1970, **41**: 989-1001.

13. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. **Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock.** *Chest* 1991, **99**: 956-962.

14. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC: **Early lactate clearance is associated with improved outcome in severe sepsis and septic shock**. *Crit Care Med* 2004, **32**: 1637-1642.

15. Donnino MW, Miller J, Goyal N, Loomba M, Sankey SS, Dolcourt B, Sherwin R, Otero R, Wira C: **Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients.** *Resuscitation* 2007, **75**: 229-234.

16. Peres Bota D, Melot C, Lopes Ferreira F, Nguyen Ba V, Vincent JL: **The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction.** *Intensive Care Med* 2002, **28**: 1619-1624.

17. Cabré L, Mancebo J, Solsona JF, Saura P, Gich I, Blanch L, Carrasco G, Martín MC; and the Bioethics Working Group of the SEMICYUC: **Bioethics Working Group of the SEMICYUC: Multicenter study of the multiple organ dysfunction syndrome in intensive care units: the usefulness of the Sequential Organ Failure Assessment scores in decision making.** *Intensive Care Med* 2005, **31**: 927-93.

18. Vincent JL, de Mendonca A, Cantraune F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S: **Use of the SOFA score to assess the incidence of organ system dysfunction/failure in intensive care units: results of a multi-center, prospective study**. *Crit Care Med 1998*, **26**: 1793-1800.

19. Knaus WA, Draper EA, Wagner DP, Zimmermann JE: **APACHE II A severity of disease classification system**. *Crit Care Med* 1985, **13**: 818-829.

20. DeLong ER, DeLong DM, Clarke-Pearse DL: **Comparing the areas under two or more correlated receiver operating charactistic curves: a nonparametric approach.** *Biometric* 1988, **44**: 837-845.

21. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; EMShockNet Investigators: **Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial**. *JAMA* 2010, **303**: 739-746.

22. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; for the Early Goal-Directed Therapy Collaborative Group: **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**: 1368-1377.

23. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, marshall J, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; for Surviving Sepsis Campaign: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**:858-873.

24. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI: **Occult hypoperfusion and mortality in patients with suspected infection**. *Intensive Care Med* 2007, **33**: 1892-1899.

25. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, Bellamy SL, Christie JD: **Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock**. *Crit Care Med* 2009, **37**: 1670-1677.

26. van Beest PA, Mulder PJ, Bambang Oetomo S, Van den Broek B, Kuiper MA, Spronk PE: **Measurement of lactate in a prehospital setting is related to outcome.** *Eur J Emerg Med* 2009, **16**: 318-322.

27. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, Davies A, Stachowski E, Reade MC, Baily M, Cooper DJ: **Relative hyperlactataemia and hospital mortality in critically ill patients: a retrospective multi-centre study**. *Crit Care* 2010, **14**: R25.

28. Nichol A, Baily M, Egi M, Pettila V, French C, Stachowski E, Reade MC, Cooper DJ, Bellomo R: **Dynamic lactate indices as predictors of outcome in critically ill patients**. *Crit Care* 2011, **15**: R242.

29. Friesecke S, Abel P, Roser M, Felix SB, Runge S: **Outcome of severe lactic acidosis associated with metformin accumulation.** *Crit Care* 2010, **14**: R226.

30. Protti A, Russo R, Tagliabue P, Vecchio S, Singer M, Rudiger A, Foti G, Rossi A, Mistraletti, Gattinoni: **Oxygen consumption is depressed in patients with lactic acidosis due to biguanide intoxication.** *Crit Care* 2010, **14**: R22.

Chapter 7

Veno-arterial PCO_2 difference as a tool in resuscitation of septic patients

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Abstract

Purpose To investigate the interchangeability of mixed and central venous-to-arterial carbon dioxide differences and the relation between the central venous-to-arterial carbon dioxide differences (pCO_2 gap) and cardiac index (CI). We also investigated the value of the pCO_2 gap in outcome prediction.

Methods We performed a post-hoc analysis of a well-defined population of 53 patients with severe sepsis or septic shock. Mixed and central venous pCO_2 were determined earlier at a 6-hour interval (T=0 to T=4) during the first 24 hours after intensive care unit (ICU) admittance. The population was divided into two groups based on pCO_2 gap (cut off value 0.8 kPa).

Results The mixed pCO_2 difference underestimated the central pCO_2 difference by a mean bias of 0.03 kPa ± 0.32 kPa (95% limits of agreement: -0.62 kPa to 0.58 kPa). We observed a weak relation between pCO_2 gap and CI. The in hospital mortality rate was 21% (6/29) for low gap group and 29% (7/24) for high gap group; Odds ratio 1.6 (95% CI 0.5-5.5), p = 0.53. At T=4 the Odds ratio was 5.3 (95% CI 0.9-30.7); p=0.08.

Conclusions The central venous pCO_2 should not be used as surrogate for the mixed venous pCO_2 in patients with severe sepsis or septic shock. The likelihood of bad outcome enhances when a high pCO_2 gap persists after 24 hours of therapy.

Introduction

Shock is defined as global tissue hypoxia secondary to an imbalance between systemic oxygen delivery (DO_2) and oxygen demand (VO_2). Global tissue hypoxia as a result of systemic inflammatory response or circulatory failure is an important indicator of serious illness preceding multiple organ failure. The development of organ failure predicts outcome of the septic patient [1]. Unrecognized and untreated global tissue hypoxia increases morbidity and mortality: decreased mixed venous oxygen saturation (SvO_2) values or central venous oxygen saturation ($ScvO_2$) values predict poor prognosis in septic shock [2,3]. However, in the majority of patients with severe sepsis or septic shock who are acutely admitted to the intensive care unit (ICU) $ScvO_2$ values are >70% [4,5]. Hence, normal $ScvO_2$ values do not guarantee adequate tissue oxygenation and other circulatory parameters are needed to evaluate resuscitation efforts.

A variable that has been described in this context is the central venous-to-arterial carbon dioxide difference (pCO_2 gap) [6]. Under physiological conditions, venous-to-arterial carbon dioxide difference usually does not exceed 0.8 kPa (6 mmHg) [7] and reflects adequacy of venous blood flow, i.e. cardiac output (CO) [8,9]. On macro-circulatory level, an inverse relationship between pCO_2 gap and cardiac index (CI) has been described in critically ill patients [10,11]. Indeed, in patients who fulfilled resuscitation endpoints according to international guidelines [1] a cutoff value for pCO_2 gap of 0.8 kPa discriminated between high and low lactate clearance and CI [6]. Thus, combining $ScvO_2$ values as surrogate for global tissue hypoxia and pCO_2 gap as surrogate for CI may be useful during resuscitation of critically ill patients. However in patients with severe sepsis, on the microcirculatory level distributive changes may be independent of CO [12,13]. This means that, on a regional level, in accordance to the possibility of persistent tissue hypoxia despite normal $ScvO_2$ levels, accumulation of carbon dioxide (CO_2) may occur in sepsis despite adequate CO.

In line with investigations on the agreement between SvO_2 and $ScvO_2$, it seems useful to determine whether an agreement between mixed and central venous-to-arterial carbon dioxide difference in septic patients exists [5,11]. In other words, are mixed and central venous-to-arterial carbon dioxide difference interchangeable?

We examined the relationship between central venous-to-arterial carbon dioxide difference and CI and we addressed the question whether central venous-to-arterial carbon dioxide differences are of additional value in outcome prediction. Additionally, we investigated the agreement between mixed and central venous-to-arterial carbon dioxide difference in a well defined population of patients with severe sepsis or septic shock [5].

Methods

Setting

We studied ICU populations in two teaching hospitals: the Martini Hospital [Groningen, The Netherlands] (MH) with a 14-bed “closed format” mixed medical / surgical ICU department and the Medical Center Leeuwarden [Leeuwarden, The Netherlands] (MCL) with a 16-bed “closed format” mixed medical / surgical ICU, including cardiothoracic patients. Previously, written informed consent was obtained in all cases from the patient or from the patient’s legal representative. The use of earlier obtained data [5] was approved by both Local Ethics Committees.

Patients and data collection

This post-hoc analysis of data from a prospective observational study included a population of patients we have described before [5]. All patients were 18 years or older, with sepsis or septic shock according to international criteria as the principal reason for ICU

admittance [14]. Patients were included in case of a clinical indication for additional hemodynamic monitoring using a pulmonary artery catheter (PAC) [Criticath SP 5507H TD, Becton Dickinson, Singapore] or a Continuous Cardiac Output (CCO) catheter [Arrow Deutschland GmbH, Erding, Germany]. The catheter was inserted into an internal jugular or subclavian vein according to standard procedure. Position was confirmed by the presence of pulmonary artery pressure tracings and chest radiography. Primary data, including hemodynamic variables, were collected at 6-hour interval (T0, T1, T2, T3, T4) during the first 24 hours after acute ICU admittance. Standard blood samples of 2 ml were drawn simultaneously from arterial line, distal (pulmonary artery; PA) and proximal / side portal (superior caval vein; SCV) from PAC or CCO catheter. To avoid falsely high readings due to aspiration of pulmonary capillary blood, aspiration was done gently to avoid high negative pressure when blood samples were taken. Blood was sampled from the proximal port of the catheter as representative of central venous blood [15,16]. All blood samples were analyzed by a point-of-care co-oximeter (Radiometer ABL800 flex, Copenhagen, Denmark) available in both ICU's. The Acute Physiology, Age and Chronic Health Evaluation (APACHE) II-score after 24 hours of ICU admittance was calculated [17].

Statistical analysis

For analysis the population was divided into two groups: patients with a low pCO_2 gap (<0.8kPa) vs. patients with a high pCO_2 gap (>0.8kPa) at ICU admission (T=0). Statistical tests were two-tailed and performed by the statistical package for the social sciences (IBM SPSS 19 for Windows, Chicago, IL, USA) or MedCalc software (version 11.2.1, Mariakerke, Belgium) for comparing ROC curves. GraphPad software (Prism 5.0, La Jolla, CA, USA) was used for graphics. Measurements were not independent but clustered within each patient. All data were tested for normal distribution with the D'Agostino-Pearson omnibus normality test before further statistical analysis. Differences between both groups were assessed using

Student's t-test in case of normal distribution. For categorical data Chi-Square test or Fisher's exact test was used. For each time point (T0-T4) the difference between arterial CO_2 partial pressure ($paCO_2$) and central venous ($pvCO_2$), i.e. pCO_2 gap was calculated. Also, for each time point the average of CI, mean arterial pressure (MAP), $ScvO_2$, lactate, and infusion rate of both norepinephrine and dopamine was calculated. The agreement between CI and pCO_2 gap was assessed by the mean bias and 95% limits of agreement (mean bias ± 1.96 x standard deviation) as described by Bland and Altman (BA) [18]. Pearson correlation coefficient between mixed and central venous pCO_2 differences was determined. Finally, the odds ratio for mortality between patients with a high pCO_2 gap and patients with a low pCO_2 gap at both T=0 and T=4 was calculated. Data are displayed as mean ± SD. Statistical significance was assumed at $p < 0.05$.

Results

We enrolled 56 patients, of whom three patients were excluded due to lack of data (technical problems). We evaluated data from 53 patients with sepsis. Thirty patients were enrolled at MCL and 23 patients were enrolled at MH. No complications other than transient arrhythmias were observed during the insertion of any catheter.

Altogether 245 paired blood samples were obtained. At T=0, 29 patients had a central pCO_2 difference less than 0.8 kPa (low gap group), and 24 patients had a central pCO_2 difference larger than 0.8 kPa (high gap group). Baseline characteristics and outcome of the total population and both groups are shown in table 1. Length of stay at the ICU (LOS_{ICU}) was 12 ± 10 days and length of stay at the hospital (LOS_{HOSP}) was 25 ± 18 days.

Table 1. Baseline characteristics

variable	total population (n=53)	low gap (n=29)	high gap (n=24)	P value [#]
age (yr)	66 ± 12	67 ± 13	66 ± 11	0.83
gender (m/f)	28 / 25	17 / 12	11 / 13	0.41 [1)]
APACHE II	27 ± 8	26 ± 7	27 ± 9	0.70
diagnosis				0.78 [1)]
abdominal	25	13	9	
respiratory	16	10	7	
urological	5	2	3	
other	7	4	5	
therapy				
mechanical ventilation	52 / 53	28 / 29	24 / 24	1.00 [2)]
RRT	15 / 53	5 / 29	10 / 24	0.08 [2)]
dopamine (µg/kg/min)	4.1 ± 3.9	3.6 ± 3.5	4.8 ± 2.7	0.41
norepinephrine (µg/kg/min)	0.20 ± 0.18	0.23 ± 0.23	0.16 ± 0.19	0.35
MAP (mmHg)	66 ± 10	68 ± 9	63 ± 11	0.11
CVP (mmHg)	12 ± 6	12 ± 5	13 ± 6	0.38
CI (L/min/m^2)	3.7 ± 1.2	4.1 ± 1.1	3.3 ± 1.1	0.01 [*]
lactate (mmol/L)	3.3± 3.0	2.8 ± 3.1	3.9 ± 2.9	0.19
$ScvO_2$ (%)	71.8 ± 10.1	74.5 ± 9.3	71.1 ± 7.1	< 0.001 [*]
SvO_2 (%)	71.9 ± 10.7	73.2 ± 9.1	70.3 ± 6.6	< 0.01 [*]
pCO_2 difference (kPa)	0.70 ± 0.52	0.38 ± 0.42	1.10 ± 0.33	< 0.001 [*]
hematocrit (%)	31 ± 1	30 ± 5	31 ± 6	0.49
SaO_2 (%)	96 ± 2	97 ± 2	96 ± 3	0.37
pH	7.30 ± 0.10	7.31 ± 0.09	7.29 ± 0.11	0.59

Data are presented as mean ± SD or as numbers; [#] low gap vs. high gap group; APACHE II, acute physiology, age and chronic health evaluation; RRT, renal replacement therapy; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; SaO_2, arterial oxygen saturation; [1)] Fisher's exact test; [2)] Chi Square test; [*] statistically significant difference

Agreement mixed and central pCO_2 difference

The mixed pCO_2 difference underestimated the central pCO_2 difference by a mean bias (or absolute difference) of 0.03 ± 0.32 kPa in all paired measurements. The 95% limits of agreement ranged from -0.62 to 0.58 kPa (figure 1). Correlation was significant ($p < 0.001$) with Pearson correlation coefficient r of 0.57. Mean delta was not significantly different from 0 ($p = 0.11$): both values tend to be equal. This was confirmed by an intra-class coefficient between the mixed and central pCO_2 differences of 0.70 ($p < 0.001$).

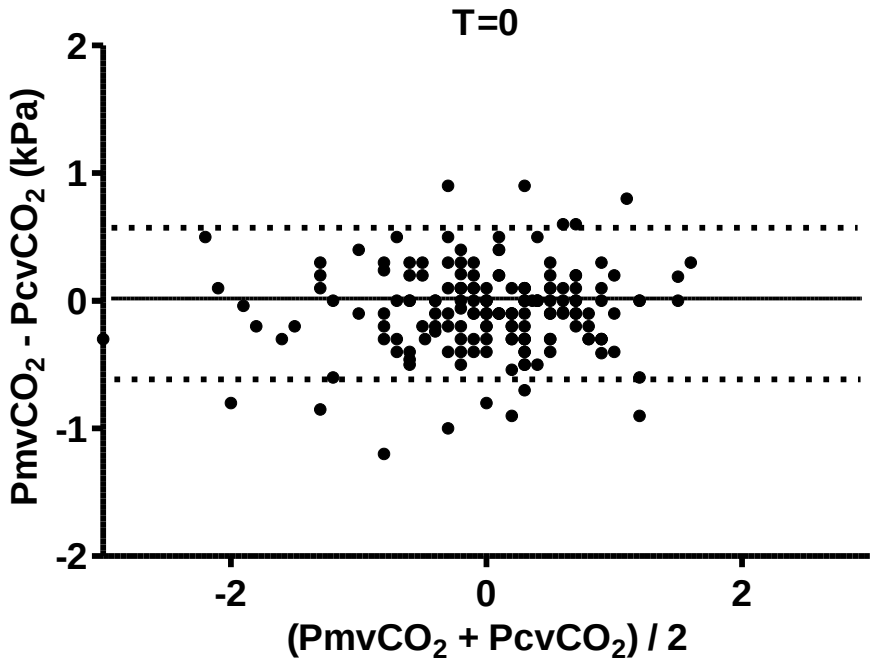

Figure 1. Bland and Altman plots showing the agreement between mixed venous pCO_2 ($PmvCO_2$) and central venous pCO_2 ($PcvCO_2$) at T=0. Mean bias 0.03 ± 0.32 kPa; 95% limits of agreement from -0.62 to 0.58 kPa.

The results at various time points were similar with at T=0 a mean bias of -0.13 ± 0.40 kPa and 95% limits of agreement of -1.0 to 0.8 kPa.

When the central pCO_2 difference was plotted against CI for all paired measurements, there was an inverse logarithmic relationship with increasing central pCO_2 difference as CI decreased (regression equation: $CO_2gap = 10^{(-0.90\ CI + 0.07)}$; $R^2 = 0.07$ $p < 0.0001$; figure 2).

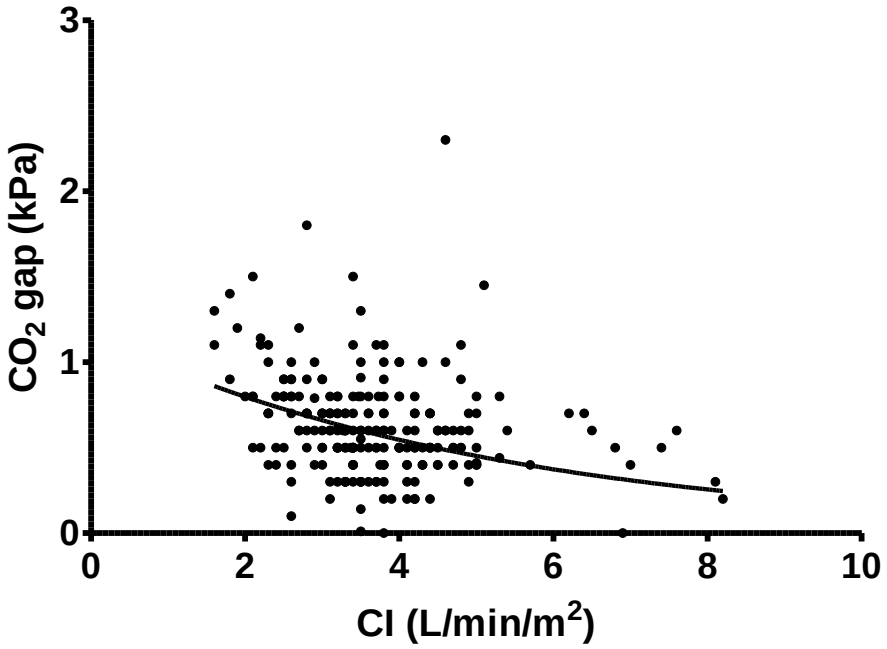

Figure 2. Correlation between central venous pCO_2 difference and cardiac index in total population for all paired measurements at T=0. $R^2 = 0.07$; $p < 0.0001$.

Differences between low gap and high gap group

At T=0, low gap group patients had a significantly lower pCO_2 gap than patients of the high gap group (0.38 ± 0.42 kPa vs. 1.10 ± 0.33 kPa; $p < 0.001$). There was no significant difference between the two groups for age, gender, APACHE II, diagnosis and treatment received (table 1). The groups did not differ in both arterial blood pressure with equivalent inotropic doses and degree of hyperlactaemia. CI was significantly lower in the high gap group (3.3 ± 1.1 L/min/m^2 vs. 4.1 ± 1.1 L/min/m^2; $p = 0.01$).

Figure 3 shows the evolution in time of the central pCO_2 difference and CI. During the first 24 hours of treatment there was no significant difference in $ScvO_2$ (except for T=0), MAP, and lactate. At all time points, there was no significant difference in either norepinephrine and dopamine infusion rate or the number of patients receiving these catecholamines.

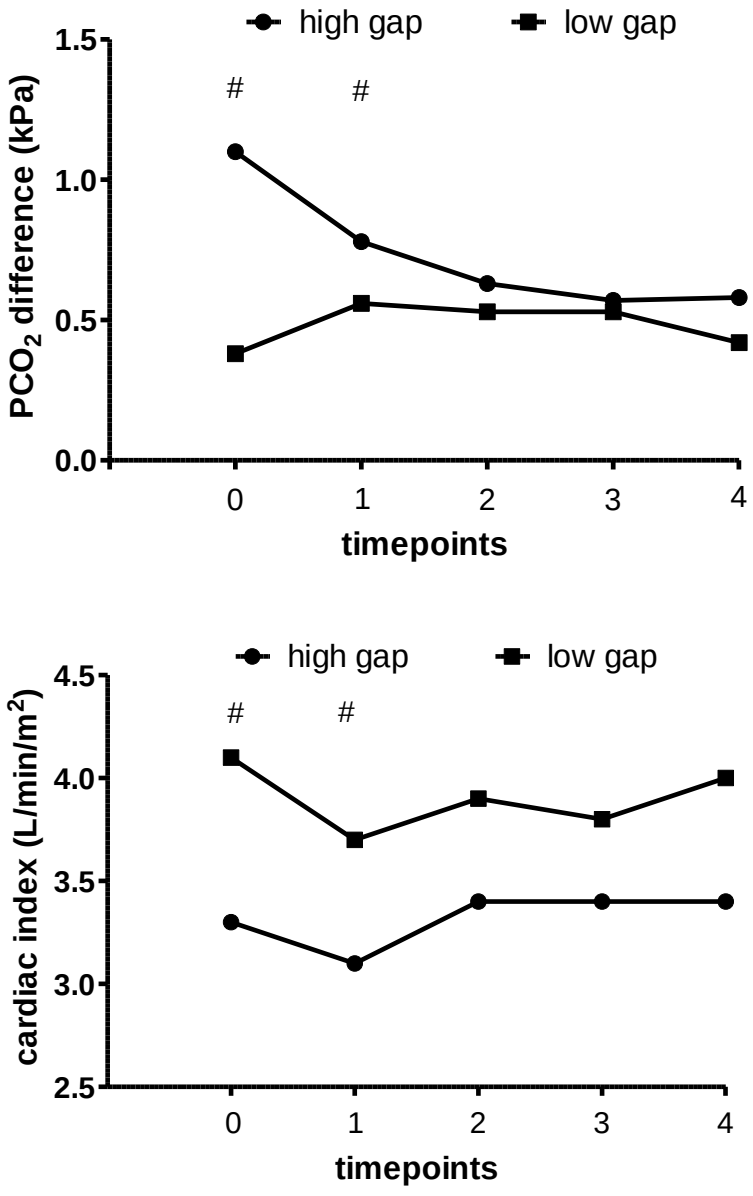

Figure 3. Evolution in time of central pCO_2 difference and cardiac index for both high gap and low gap group; time interval between time points: 6 hours. #, statistically significant difference.

Outcome

The hospital mortality rate for all patients was 24.5% (13/53). The in hospital mortality rate was 21% (6/29) for low gap group and 29% (7/24) for high gap group; Odds ratio 1.6 (95% CI 0.5-5.5), p = 0.53. Patients with a central pCO_2 difference larger than 0.8kPa at T=4 had a higher mortality change (n=8; in hospital mortality 38%) compared to patients with a central pCO_2 difference smaller than 0.8kPa at T=4 (n=39; in hospital mortality 10%): Odds ratio 5.3 (95% CI 0.9-30.7); p=0.08.

Discussion

We observed a strong agreement between the mixed venous pCO_2 and the central venous pCO_2 differences with seemingly relatively small limits of agreement in patients with severe sepsis or septic shock. From a practical perspective, the clinical utility of central pCO_2 values is of potential interest in determining the venous-arterial pCO_2 difference. The present BA analysis implacably demonstrates a strong agreement between mixed and central venous pCO_2 differences. This in line with recent findings by Cuschieri et al. who described a mixed population of critically ill patients, including patients with circulatory and cardiogenic shock. They observed a minimal but significant difference with slightly higher mean mixed pCO_2 values compared to mean central pCO_2 values (difference 0.02kPa) [11]. Similarly, we found a mean delta equal to zero. Despite the practical attractiveness of the abovementioned observations, we believe that the 95% limits of agreement (-0.62 to 0.58 kPa; and -1.0 to 0.8 kPa at T=0) are relatively wide compared to the clinical relevant cutoff value of 0.8 kPa. This means that both central venous pCO_2 values as well as mixed venous pCO_2 values may be used for the calculation of a venous-arterial pCO_2 difference, but that clinicians should not interchange these variables during treatment.

We observed a weak but significant inverse logarithmic relation between the pCO_2 gap and global blood flow, i.e. CI, in this specific sepsis population. Indeed, this is in line with

physiological theory, which describes an inverse curvilineair relation between cardiac output and pCO_2 difference, according to a modified Fick equation for a range of CO_2-production-isopleths [19]. Various studies described such an inverse relationship between mixed venous-arterial pCO_2 difference and CI in septic circulatory failure [20-22]. The increase in the venous-arterial pCO_2 gradient is explained by a inadequate washout of CO_2. Hence, a low-flow state is characterized by failure in oxygen delivery to the tissues and excesses of CO_2 in venous blood. In addition to this, in sepsis an increase in pCO_2 difference may persist in higher ranges of cardiac output. Due to heterogeneity of microcirculatory blood flow, inadequate washout of CO_2 in microcirculatory weakunits, despite normal of even elevated cardiac output, has been observed during sepsis [12,13]. Vallée et al. [6] tested this hypothesis in patients with septic shock, who were supposedly adequately resuscitated at the systemic level, with a $ScvO_2 \geq 70\%$ [1]. A central venous-arterial pCO_2 difference > 6 mmHg at baseline was inversely correlated with lactate clearance and reduction in SOFA score after 24 hours. This might be due to the observed significant lower cardiac index in the high gap group, but the normal $ScvO_2$ also points towards the possibility of distributive deficits of a normal or elevated systemic blood flow. As expected [4], in our population the mean $ScvO_2$ values were higher than 70%. The far majority the patients with a high CO_2 gap at ICU admittance were in the horizontal part of the cardiac output - CO_2 gap curve, indicating the relative independence of the two variables in this particular range of systemic blood flow.

Finally, the predictive value of the pCO_2 difference for outcome is questionable. However, a modest time-dependent relationship between an increased pCO_2 difference and outcome was found. Although not significant, with the persistence of an increased pCO_2 difference the Odds ratio for bad outcome increases. Whether the significantly higher CI and $ScvO_2$ in the low pCO_2-gap group is causatively related or an epiphenomenon remains topic of debate, since protocols that aim for supranormal values have been proven to be harmful in critically ill patients [23,24].

This study has limitations. First, this is a multicenter, post-hoc study, and its observational character has clear limitations. Second, statements about any impact on therapeutic intervention are not possible. Third, since all patients were septic, our findings may not be generalized to patients less critically ill or to those with other forms of shock. Finally, lack of clear insight of treatment prior to ICU admittance at the different EDs or wards is a limitation of our study as well. Nevertheless, since we aimed at the usefulness of the central venous CO_2 difference after ICU admittance, we think these factors are not pertinent to the results.

Conclusion

Both central venous pCO_2 values as well as mixed venous pCO_2 values may be used for the calculation of a venous-arterial pCO_2 difference, but they should not be interchangeably during treatment of patients with severe sepsis or septic shock.

The central venous pCO_2 difference correlates with CI but should not be used to estimate CI in patients with severe sepsis and septic shock.

A priori, the predictive value for outcome of the central venous pCO_2 difference is questionable but persistence of an increased central venous pCO_2 difference after 24 hours of therapy enhances the likelihood of bad outcome.

References.

1. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall J, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM. for Surviving Sepsis Campaign: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock**. *Crit Care Med* 2004, **32**: 858-873.
2. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF: **Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events**. *Chest* 1993, **103**: 900-906.
3. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Tomlanovich M; **Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345**: 1368-1377.
4. van Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk PE, Kuiper MA: **The incidence of low venous oxygen saturation on admission in the ICU: a multicenter observational study in the Netherlands**. *Crit Care* 2008, **12**: R33.
5. van Beest PA, van Ingen J, Boerma EC, Holman ND, Groen H, Koopmans M, Spronk PE, Kuiper MA: **No agreement of mixed venous and central venous saturation in sepsis, independent of sepsis origin**. *Crit Care* 2010, **14**: R219.
6. Vallée F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii, Fourcade O, Genestal: **Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock?** *Intensive Care Med* 2008, **34**: 2218-2225.
7. Guyton AC, Hall JE: **Transport of oxygen and carbon dioxide in the blood and body fluids**. In: Guyton AC (ed) Textbook of medical physiology, 10th edn. WB Saunders Co, Philidelphia, 2000; pp 463-472.
8. Johnson BA, Weil MH: **Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses**. *Crit Care Med* 1991, **19**: 1432-1438.
9. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI: **Difference in acid-based state between venous and arterial blood during cardiopulmonary resuscitation**. *N Engl J Med* 1986, **315**: 153-156.

10. Durkin R, Gergits MA, Reed JF, Fitzgibbons J: **The relationship between arteriovenous carbon dioxide gradient and cardiac index**. *J Crit Care* 1993, **8**: 217-221.

11. Cuschieri J, Rivers EP, Donnino MW, Katilius M, Jacobson G, Nguyen HB, Pamukov N, Horst HM: **Central venous-arterial carbon dioxide difference as an indicator of cardiac index**. *Intensive Care Med* 2005, **31**: 818-822.

12. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL: **Sublingual capnometry tracks microcirculatory changes in septic patients**. *Intensive Care Med* 2006, **32**: 516-523.

13. Fries M, Weil MH, Sun S, Huang L, Fang X, Cammarata G, Castillo C, Tang W: **Increases in tissue PCO_2 during circulatory shock reflect selective decreases in capillary blood flow**. *Crit Care Med* 2006, **34**: 446-452.

14. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G: 2001 **SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference**. *Intensive Care Med* 2003, **29**: 530-538.

15. Chwala LS, Zia H, Guttierez G, Katz NM, Seneff MG, Shah M: **Lack of equivalence between central and mixed venous oxygen saturation.** *Chest* 2004, **126**: 1891-1896.

16. Gutierrez G, Comignanni P, Huespe L, Hurtado FJ, Dubin A, Jha V, Arzani Y, Lazzeri S, Sosa L, Riva J, Kohn W, Suarez D, Lacuesta G, Olmos D, Mizdraji C, Ojeda A: **Central venous to mixed venous blood oxygen and lactate gradients are associated with outcome in critically ill patients**. *Intensive Care Med* 2008, **34**: 1662-1668.

17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system.** *Crit Care Med* 1985, **13**: 818-829.

18. Bland JM, Altman DG: **Agreement between methods of measurement with multiple observations per individual.** *J Biopharm Stat* 2007, **17**: 571-582.

19. Lamia B, Monnet X, Teboul JL: **Meaning of arterio-venous PCO_2 difference in circulatory shock**. *Minerva Anesthesiol* 2006, **72**: 597-604.

20. Mecher CE, Rackow EC, Astiz ME, Weil MH: **Venous hypercarbia associated with severe sepsis and systemic hypoperfusion**. *Crit Care Med* 1990, **18**: 585-589.

21. Bakker J, Vincent JL, Gris Ph, Leon M, Coffernils M, Kahn RJ: **Veno-arterial carbon dioxide gradient in human septic shock.** *Chest* 1992, **101**: 509-515.

22. Rackow EC, Astiz ME, Mecher CE, Weil MH: **Increased venous-arterial carbon dioxide tension difference during severe sepsis in rats**. *Crit Care Med* 1994, **22**: 121-125.

23. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R – SvO_2 collaborative group: **A trial of goal-oriented hemodynamic therapy in critically ill patients**. *N Engl J Med* 1995, **333**: 1025-1032.

24. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D: **Elevation of systemic oxygen delivery in the treatment of critically ill patients**. *N Engl J Med* 1994, **330**: 1717-1722.

Chapter 8

Summary

The majority of patients described in the present thesis were admitted at the various hospitals and ICUs with severe sepsis or septic shock. Sepsis is a syndrome characterized by infection acompanied by a systemic inflammatory response syndrome (SIRS), i.e. a generalized condition which affects the entire body. With increasing seriousness organs fail and (relative) hypotension occurs. The complexity of the pathophysiology of sepsis demands treatment strategies that covers much more than just the prescription of the right antibiotic to eliminate the source, e.g. bacteria. One crucial part of therapy is hemodynamic optimization of the patient. This is recognized by the international Surviving Sepsis Campaign by embracing the EGDT strategy [1]. Indeed, one can argue on the implementation of a single center strategy in international guidelines [2,3] but this discussion may never blur the notion of the strategy itself. Of course, goal-oriented manipulation of cardiac preload, afterload and contractility, including $ScvO_2$ monitoring is a valuable strategy in a subset of patients. The results presented in chapter 2 subscribe this: early identification of patients at risk for cardiovascular collapse is important as illustrated by the high mortality rate (57%) in the small subset of patients with an initial $ScvO_2$ <50%. Hence, low $ScvO_2$ values do exist early after ICU admittance, but apparently its incidence is very low (chapter 2) which makes generalized EGDT application a premature activity [2]. However, to ignore a valuable strategy such as EGDT at this stage may be an unwise thing to do. EGDT implies early recognition of the critically ill patient and enforces continuous reassessment of treatment [4] which is probably one of the greatest gains in treating patients with severe sepsis or septic shock over the last decade. This also implies that irrespective of proper EGDT treatment the clinician should not rest on his or her laurels once several treatment goals have been achieved.

When a clinician sets several treatment goals, he or she should be aware of the value of each goal used. Thus, pursuing abstract numbers without comprehension of their relevance should be avoided. It should also not be considered to assume that a $ScvO_2$ value of 70% automatically means a SvO_2 value of 65% in patients with severe sepsis or septic

shock. As applies to the trends of both values, the agreement between both absolute values is unacceptably wide which means that $ScvO_2$ does not reliably predict SvO_2 (chapter 3). The difference is not a fixed 5% as stated in many text books and both values should not be considered numerically equal. This is not only of academic importance [5] but also clinically relevant [6]. If one abandons SvO_2 and uses $ScvO_2$ in the resuscitation of critically patients one should be aware that also information on pulmonary artery pressures, cardiac filling pressures, and cardiac output is disposed. Nevertheless, alternative less invasive hemodynamic monitoring devices such as transoesophageal echocardiography, PiCCO, and Flo Trac are available [7,8]. With the use of these devices PAC-related complications can be avoided [9].

The abovementioned lack of agreement between $ScvO_2$ and SvO_2 values does not exclude the clinical use of both values separately. In line with earlier work [10], $ScvO_2$ values in nonsurvivors fell more frequently below the cutoff value of 70% compared to survivors and SvO_2 values below 65% were more frequently found in nonsurvivors compared to survivors. This suggests that after the first hours of resuscitation monitoring of venous oxygen saturations could still be clinically relevant.

When a central venous access via the jugular or subclavian vein is impossible a relatively easy and safe option is central venous access via the femoral vein. The femoral central venous line is an adequate route for administration of e.g. antibiotics or catecholamines, although the risk for infectious and thrombotic complications should be kept in mind [11]. However, it is not an adequate site to obtain data as a surrogate for $ScvO_2$ values (chapter 4): $SfvO_2$ cannot replace $ScvO_2$. This is not only the case during surgery or resuscitation of critically ill patients, including patients with septic shock, but also in stable conditions. Thus ease, or incompetence, should never be a surrogate for good data. Hopefully the data are convincing enough to abandon such practice in the future.

Treatment of shock implies improvement of the circulatory state with redistribution of flow. Illustratively, four cases are mentioned in chapter 4 in which $SfvO_2$ decreased after six hours of treatment while $ScvO_2$ increased. Three out of these four patients died. Although not sufficiently powered, this underlines the urgency of shock treatment and the possible consequences when a patient does not respond to treatment.

Before treatment, (septic) shock should be recognized as early as possible. Delayed identification of global tissue hypoxia increases morbidity and mortality. When paramedics can recognize critically ill patients better, they will be able not only to start treatment early but also to inform ED personnel so appropriate measures can be taken. Vital signs are not always accurate enough to detect global tissue hypoxia. Lactate however, rarely transcends 4 mmol/L in not critically ill patients and lactate also seems a useful additional risk stratification tool [14-16]. Fortunately, the implementation of prehospital lactate measurement is feasible (chapter 5). Unfortunately, less deteriorated hemodynamics does not trigger the average paramedic to obtain a lactate measurement. This makes the implementation difficult and strenuous efforts are necessary to train personnel on the use of early lactate measurement. The results presented in chapter 5 are in line with earlier findings [17] and support the conclusion that early lactate determination is helpful in early triage decisions. With the present results in mind should we abolish measurement of vital signs and ignore clinical presentation? Absolutely not: one should take both vitals and a lactate into account.

In the setting of the ICU it is common practice to take a lactate measurement. However, the frequency of measurement varies in clinical practice. Especially during the first hours of treatment regular measurements seem useful as part of reassessment. Indeed, increased clearance during the first six resuscitation hours means better survival [18]. But does the value of lactate evaporate after the first hours of ICU admittance? No: on-going watchfulness is the order. Despite equivalent specificities and sensitivities for predicting in-hospital mortality, not only lactate at admission but also lactate-derived variables were significantly different between survivors and nonsurvivors (chapter 6). In addition,

persistence of hyperlactataemia was associated with organ failure expressed in (cumulative) SOFA points. This provides a link to clinical practice and subscribes the use of lactate as a risk-stratification tool [16].

How sensitive is lactate as a warning signal for organ failure and outcome? This partly depends on the cut off point. The choice in chapter 6 for the threshold of 2.2 mmol/L (upper normal limit) was a deliberate one. First, the goal is to 'normalize' the patients' status and second, also moderate elevated lactate levels decrease survival chances [1,17,19]. Another issue in this context is the mechanism causing hyperlactataemia which is probably more important than the hyperlactataemia itself [20-22]. Hence, the question on predictive sensitivity is difficult to answer and maybe not important. Of note, presence of hyperlactataemia in ICU patients is important and should encourage the clinician to reflection. To put the hyperlactataemia in perspective, the clinical picture, hemodynamics, $ScvO_2$, and vital signs should be considered.

During treatment of critically ill patients and the regular reassessment of this treatment $ScvO_2$ and lactate are useful but not perfect tools. The pCO_2 gap described in chapter 7 may indeed be a welcome additional application. This variable indirectly estimates systemic blood flow and may help to identify the patients who remain inadequately resuscitated [23]. When the pCO_2 gap is used in clinical practice central venous and mixed venous pCO_2 values should not be used interchangeably for calculation of venous-arterial pCO_2 difference: although the 95% limits of agreement seem attractively small, they are relatively wide (chapter 7).

A high pCO_2 gap (> 0.8 kPa or > 6 mmHg) at ICU admission may be indicative for low lactate clearance and limited reduction in SOFA score after 24 hours of treatment [23]. On top of that, when the pCO_2 gap remains high after 24 hours of treatment survival chances seem to diminish (chapter 7). However, these results do not warrant the use of pCO_2 difference in future treatment algorithms.

Taken together, the following conclusions can be derived from the studies described in this thesis:

- The incidence of low $ScvO_2$ values of acutely admitted critically ill patients is low in Dutch ICUs. This is especially true for patients with sepsis or septic shock.
- In our setting, use of $ScvO_2$-guided resuscitation may only be helpful in a small subset of sepsis.
- Mean SvO_2 values and mean $ScvO_2$ values in acutely admitted critically ill patients, including patients with severe sepsis or septic shock, are in the normal range in our ICUs.
- $ScvO_2$ does not reliably predict SvO_2 in patients with sepsis, independent of sepsis origin.
- The change of $ScvO_2$ compared to the change of SvO_2 is not more reliable than the exact numerical values in patients with sepsis.
- $SfvO_2$ cannot replace $ScvO_2$, neither in stable conditions nor during surgery or during the resuscitation phase in critically ill patients.

- The implementation of lactate measurement in pre-hospital setting is feasible and potentially clinical relevant, albeit difficult. Subsequent studies should evaluate if treatment based on pre-hospital lactate measurement will improve outcome.
- Persistence of hyperlactataemia is associated with organ failure expressed in (cumulative) SOFA points.

- Lactate load is associated with in-hospital mortality in a heterogeneous ICU population.

- The central venous pCO_2 should not be used as surrogate for the mixed venous pCO_2 in patients with severe sepsis or septic shock.

- A priori, the predictive value for outcome of the central venous pCO_2 difference is questionable but persistence of an increased central venous pCO_2 difference after 24 hours of therapy seem to enhance the likelihood of bad outcome in patients with severe sepsis or septic shock.

References

1. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, marshall J, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; for Surviving Sepsis Campaign: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**:858-873.
2. Bellomo R, Reade MC, Warrillow SJ: **The pursuit of high central venous oxygen saturation in sepsis: growing concerns.** *Crit Care* 2008, **12**: 130.
3. Perel A: Bench-to-bedside review: **The initial hemodynamic resuscitation of the septic patient according to Surviving Sepsis Campaign guidelines - does one size fit all?** *Crit Care* 2008, **12**: 223.
4. Nguyen HB, Corbett SW, Steele R, Banta J, Clark RT, Hayes SR, Edwards J, Cho TW, Wittlake WA: **Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality**. *Crit Care Med* 2007; **35**: 1105-1112.
5. Rivers E: **Mixed vs central venous oxygen saturation may be not numerically equal, but both are still clinically useful**. *Chest* 2006, **129**:507-508
6. Vincent JL: **So we use less pulmonary artery catheters – but why?** Crit Care Med 2011, 39: 1820-1821.
7. Field LC, Guldan III GJ, Finley AC: **Echocardiography in the intensive care unit**. *Sem Cardiothor Vasc Anesth* 2011, **15**: 25-39
8. Hadian M, Kim HK, Severyn DA, Pinsky MR: **Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, Flo Trac and pulmonary artery catheter**. *Crit Care* 2010, **14**: R212
9. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell Jr FE, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson Jr WJ, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA: **The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT investigators**. *JAMA* 1996, **276**: 889-897.
10. Reinhart K, Kuhn HJ, Hartog C, Bredle DL: **Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill**. *Intensive Care Med* 2004, **30**: 1572-1578.

11. Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E, Rigaud JP, Casciani D, Misset B, Bosquet C, Outin H, Brun-Buisson C, Nitenberg G: **Complications of femoral and subclavian venous catheterization in critcailly ill patients**. *JAMA* 2001, **286**: 700-707.

12. Rady MY, Rivers EP, Novak RM: Resuscitation of the critically ill in the ED: **responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate.** *Am J Emerg Med* 1996, **14**: 218-225.

13. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B: **Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units; French ICU Group for Severe Sepsis**: *JAMA* 1995, **274**: 968-974.

14. Kruse JA, Zaidi SA, Carlson RW: **Significance of blood lactate levels in critically ill patients with liver disease**. *Am J Med* 1987, **83**: 77-82.

15. Bernardin G, Pradier C, Tiger F, Deloffre P, Mattei M: **Blood pressure and arterial lactate levels are early indicators of short-term survival in human septic shock**. *Intensive Care Med* 1996, **22**: 17-25.

16. Shapiro NI, Howell MD, Talmor D, Nathanson LA, Lisbon A, Wolfe RE, Weiss JW:. **Serum lactate as a predictor of mortality in emergency department patients with infection.** *Ann Emerg Med* 2005, **45**: 524-528.

17. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI: **Occult hypoperfusion and mortality in patients with suspected infection**. *Intensive Care Med* 2007, **33**: 1892-1899.

18. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, Tomlanovich MC: **Early lactate clearance is associated with improved outcome in severe sepsis and septic shock**. *Crit Care Med* 2004, **32**: 1637-1642.

19. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, Bellamy SL, Christie JD: **Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock**. *Crit Care Med* 2009, **37**: 1670-1677.

20. Friesecke S, Abel P, Roser M, Felix SB, Runge S: **Outcome of severe lactic acidosis associated with metformin accumulation.** *Crit Care* 2010, **14**: R226.

21. Protti A, Russo R, Tagliabue P, Vecchio S, Singer M, Rudiger A, Foti G, Rossi A, Mistraletti, Gattinoni: **Oxygen consumption is depressed in patients with lactic acidosis due to biguanide intoxication.** *Crit Care* 2010, **14**: R22.

22. Stacpoole PW, Wright EC, Baumgarter TG, Bersin RM, Buchalter S, Curry SH, Duncan CH, Harman EM, Henderson GN, Jenkinson S, Lachin JM, Lorenz A, Schneider SH, Siegel JH, Summer WR, Thompson D, Wolfe CL, Zorovich B: **A Controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group**. *N Engl J Med* 1992, **327**: 1564-1569.

23. Vallée F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii, Fourcade O, Genestal: **Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock?** *Intensive Care Med* 2008, **34**: 2218-2225.

Nederlandse samenvatting

De meerderheid van de patiënten hier beschreven waren op de diverse intensive care afdelingen (IC) opgenomen met ernstige sepsis of septische shock. Sepsis is een syndroom wat voortkomt uit de reacties van het lichaam, inflammatoire respons, op een infectie; het hele lichaam is hierbij betrokken. Bij toenemende ernst zullen organen minder goed gaan functioneren zodat zelfs orgaanfalen ontstaat. Indien ook de bloeddruk in bepaalde mate daalt wordt gesproken van septische shock. Vanwege de complexiteit van dit ziektebeeld vereist de behandeling veel meer dan alleen het voorschrijven en toedienen van een antibioticum. Zoals in internationale richtlijnen wordt beschreven, is het optimaliseren van de hemodynamiek belangrijk onderdeel van de behandeling. Deze aanbeveling is gebaseerd op één, overigens veelbetekende, strategie welke in één ziekenhuis werd uitgevoerd. Men kan zich inderdaad de vraag stellen of de letterlijke implementatie van deze strategie in internationale richtlijnen gewenst is. De resultaten waren indrukwekkend maar de resultaten zijn ook nooit meer in gelijke mate elders behaald. Dit neemt niet weg dat de strategie om doelgericht en op geleide van onder andere de centraal veneuze saturatie ($ScvO_2$) de cardiale 'prestatie indicatoren' (preload, afterload, contractiliteit) te verbeteren ('Early Goal-Directed Therapy', EGDT) wel degelijk een waardevolle strategie is. De resultaten beschreven in hoofdstuk 2 bevestigen dit: 57% van de patiënten met een zeer lage $ScvO_2$ (<50%; normaal waarde 70%) bij opname overleeft de sepsis niet. Dus vroege herkenning van de ernstig zieke patiënt met een hoog risico op hemodynamische ineenstorting belangrijk zodat daarna tijdens de eerste uren 'agressief' behandeld kan worden. Desalniettemin komen op Nederlandse IC's bij acute opnames van septische patiënten zeer weinig lage $ScvO_2$ waarden voor (hoofdstuk 2). Algemene introductie van EGDT lijkt dus voorbarig en zullen de resultaten van diverse grote studies verspreid over meerdere centra EGDT in perspectief plaatsen. Hiermee wordt niet geïmpliceerd dat EDGT genegeerd moet worden, in tegendeel. De arts wordt indachtig EGDT gedwongen de behandeling continue te evalueren: op zijn of haar lauweren rusten is er niet bij! Deze geprotocolleerde aanpak is een belangrijke vooruitgang in de behandeling van patiënten met ernstige sepsis of septische shock.

Wanneer een arts bepaalde behandelingsdoelen nastreeft (bijvoorbeeld normalisatie van de SvO_2) dient hij of zij zich ook bewust te zijn van de waarde van elk doel. Met andere woorden, het zonder enig begrip najagen van abstracte getallen (biologische parameters) moet worden vermeden. Zo is het eveneens onverstandig bij septische patiënten aan te nemen dat een normale $ScvO_2$ (70%) automatisch een normale gemengd veneuze saturatie (SvO_2) betekent. Beide parameters zijn fysiologisch met elkaar verbonden maar zowel de absolute waarden als de trend van beide parameters variëren te veel zodat $ScvO_2$ de SvO_2 niet betrouwbaar inschat (hoofdstuk 3). Dit is niet alleen van enig academisch belang maar is ook klinisch relevant. Het vervangen van SvO_2 waarden door $ScvO_2$ waarden impliceert dat de Swan Ganz katheter (arteria pulmonalis katheter; SG) waarmee de SvO_2 wordt gemeten in de kast blijft liggen. Hiermee worden de aan SG gerelateerde complicaties uiteraard vermeden, maar tegelijkertijd wordt aanvullende informatie (arteria pulmonalis drukken, cardiale vullings drukken, slagvolume) over boord gegooid.

Hoewel $ScvO_2$ en SvO_2 niet elkaars gelijke zijn, kunnen beide parameters nog steeds onafhankelijk van elkaar gebruikt worden. Gedurende de eerste 24 uur na IC opname werden meer lage $ScvO_2$ en SvO_2 waarden gezien bij patiënten die uiteindelijk in het ziekenhuis overleden (nonsurvivors) dan bij patiënten die niet overleden (survivors). Dit suggereert dat bepaling van veneuze saturaties ook ná de eerste uren relevant kan zijn.

Voor het bepalen van $ScvO_2$ of SvO_2 is een centraal veneuze toegang via de vena jugularis interna of vena subclavia nodig. Wanneer het verkrijgen van een dergelijke toegang niet lukt gecontra-indiceerd is er nog altijd een andere optie: de vena femoralis. Via deze route kunnen ook catecholaminen en antibiotica worden toegediend, waarbij wel het risico op mogelijke complicaties (infectie, thrombose) in het achterhoofd moet worden gehouden. Echter, voor het vergaren van data als surrogaat voor $ScvO_2$ is deze route ongeschikt: de femoraal veneuze saturatie ($SfvO_2$) is geen alternatief voor $ScvO_2$ (hoofdstuk 4). Dit geldt niet alleen bij kritisch zieke patiënten of patiënten die een operatie ondergaan maar zelfs ook in de poliklinische setting (hoofdstuk 4). Hopelijk zijn de data gepresenteerd in hoofdstuk 4

overtuigend genoeg om dergelijke praktijken voortaan achterwege te laten. Gemak, of zelfs incompetentie, mogen nooit leiden tot onbetrouwbare parameters.

Voordat een behandeling van ernstige sepsis of septische shock gestart kan worden moet de patiënt met een dergelijk syndroom eerst worden herkend, en liefst zo snel mogelijk. Vertraagde herkenning van weefsel hypoxie (globaal zuurstof tekort) leidt tot verhoogde morbiditeit en sterfte. Als de ziekte al door paramedici, zoals ambulance personeel, herkend kan worden is dat dus winst: de behandeling wordt snel gestart en het personeel op de Spoedeisende Hulp (SEH) kan op de komst van een kritisch zieke patiënt worden voorbereid. Conventionele parameters (bloeddruk, saturatie, hartslagfrequentie) zijn niet altijd accuraat genoeg voor detectie van weefsel hypoxie. Buiten het ziekenhuis worden geen centrale lijnen aangelegd en $ScvO_2$ kan hier dus niet gebruikt worden als surrogaat voor weefsel hypoxie. Lactaat lijkt een goed alternatief: lactaat is bij niet-kritisch zieke patiënten zelden hoger dan 4 mmol/L en lactaat is al beschreven als hulpmiddel om risico op sterfte in te schatten op een SEH. Gelukkig is de implementatie van een lactaat bepaling door ambulance personeel haalbaar (hoofdstuk 5). Helaas voelt het ambulance personeel zich echter niet altijd genegen bij patiënten met nog redelijke conventionele parameters het lactaat ook daadwerkelijk af te nemen. Dat is jammer, want juist deze patiënten populatie zou gebaat kunnen zijn bij vroege herkenning en behandeling van ziekte. Bovendien verloopt de implementatie van lactaat meting in een pre-hospitale setting hierdoor moeizaam. Overigens zijn de resultaten beschreven in hoofdstuk 5 geen vrijbrief om de conventionele parameters en klinische presentatie van de patiënt te negeren: lactaat kan een belangrijk hulpmiddel zijn.

Op de IC wordt regelmatig lactaat bepaald. Als onderdeel van een behandelingsstrategie om het lactaat binnen 6 uur te normaliseren heeft lactaat zijn reeds bewezen. Maar verdampt het nut na de eerste 6 uur? Dit lijkt het niet het geval en continue alertheid is het devies want niet alleen het lactaat bij opname is van belang maar ook hogere lactaat waarden gedurende het hele verblijf op de IC onderscheiden survivors van

nonsurvivors (hoofdstuk 7). Bovendien is een verhoogd lactaat geassocieerd met orgaan falen uitgedrukt in SOFA score, het eerste teken aan de wand van verslechtering. Hierbij moet wel worden opgemerkt dat uiteraard niet alleen naar een verhoogd lactaat (hyperlactatemie) moet worden gekeken, maar dat dit ook in perspectief moet worden geplaatst.

Uit voorgaande blijkt dat zowel $ScvO_2$ als lactaat nuttige parameters zijn tijdens de behandeling van kritisch zieke patiënten. Echter, zo is ook gebleken, beide parameters zijn niet perfect. In hoofdstuk 7 wordt nog een derde handvat aangereikt: het arterio-veneuze pCO_2 verschil (pCO_2 gap). Met behulp van de pCO_2 gap kan een inschatting worden gemaakt van de circulatie (lees: bloed flow, slagvolume): een verhoogde pCO_2 gap verraadt een verlaagd slagvolume. Bovendien kan ook de pCO_2 gap worden gebruikt om nog onvoldoende behandelde, maar niet als dusdanig herkende patiënten worden herkend. Voor de berekening kunnen zowel de centraal veneuze als gemengd veneuze pCO_2 worden gebruikt, maar beide getallen mogen niet met elkaar worden verwisseld. Met andere woorden: ze zijn niet elkaars gelijke (hoofdstuk 7). Wanneer een verhoogde pCO_2 gap na 24 uur behandeling op de IC verhoogd blijft dan daalt mogelijk de overlevingskans van de patiënt: de shock kon niet adequaat genoeg worden bestreden.

Uit de hier beschreven studies kunnen de volgende conclusies worden getrokken:

- Lage $ScvO_2$ waarden komen bij acuut opgenomen septische patiënten weinig voor.
- Resuscitatie op geleide van $ScvO_2$ lijkt vooral waardevol in een klein deel patiënten met ernstige sepsis.
- ‘Gemiddelde’ SvO_2 en $ScvO_2$ waarden bij acuut opgenomen septische patiënten zijn normaal in Nederlandse IC’s.
- $ScvO_2$ is geen betrouwbaar surrogaat voor SvO_2 bij septische patiënten; dit geldt niet alleen voor de absolute getallen maar ook voor de veranderingen.

- $SfvO_2$ mag niet gebruikt worden als surrogaat voor $ScvO_2$ bij zowel stabiele cardiale poliklinische patiënten, patiënten die chirurgie ondergaan of bij kritisch zieke patiënten.
- Het implementeren van lactaat metingen door ambulance personeel is mogelijk, moeizaam maar waarschijnlijk wel klinisch relevant.
- Voortdurende hyperlactatemie is geassocieerd met orgaan falen, uitgedrukt in SOFA score.
- Lactaat is geassocieerd met sterfte in een heterogene IC populatie.
- De centraal veneuze pCO_2 is geen surrogaat voor de gemengd veneuze pCO_2 bij patiënten met ernstige sepsis of septische shock.
- A priori is de voorspellende waarde van het centraal veneuze pCO_2 verschil (pCO_2 gap) voor sterfte nihil, maar een persisterend verhoogde pCO_2 gap na 24 uur behandeling op de IC lijkt de kans op sterfte te verhogen bij patiënten met ernstige sepsis of septische shock.

Abbreviations

AMC	Amsterdam Medical Center
APACHE II	acute physiology, age and chronic health evaluation
AUC	area under the curve
CCO	continuous cardiac output
CI	cardiac index
CI	confidence interval
CNS	central nervous system
CO	cardiac output
CO_2	carbon dioxide
CPR	cardiopulmonary resuscitation
CVC	central venous catheter
CVP	central venous pressure
DO_2	systemic oxygen delivery
ED	emergency department
EGDT	early goal-directed therapy
GCS	Glasgow Coma Scale
GDT	goal-directed therapy
GH	Gelre Hospital
Hct	hematocrit
HR	heart rate

ICU	intensive care unit
LOA	95% limits of agreement
LPA	Landelijk Protocol Ambulance
LOS_{HOSP}	length of hospital stay
LOS_{ICU}	length of ICU stay
$LOS_{ICU / CCU}$	length of intensive care unit / critical care unit stay
MAP	mean arterial pressure
MCL	Medical Center Leeuwarden
MH	Martini Hospital
MODS	multiple organ dysfunction syndrome
O_2	oxygen
O_2ER	oxygen extraction ratio
PA	pulmonary artery
PAC	pulmonary artery catheter
$PaCO_2$	arterial CO_2 partial pressure
PCO_2 gap	central venous to arterial carbon dioxide difference
$PvCO_2$	central venous CO_2 partial pressure
ROC	receiver operating characteristic
RRT	renal replacement therapy
RTS	revised trauma score

SAP	systolic arterial pressure
SAPS	simplified acute physiology score
SaO_2	arterial oxygen saturation
SCV	superior caval vein
$ScvO_2$	central venous oxygen saturation
$S(c)vO_2$	mixed / central venous oxygen saturation
($ScvO_2$ – SvO_2)	difference between $ScvO_2$ and SvO_2
$SfvO_2$	femoral venous oxygen saturation
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SvO_2	mixed venous oxygen saturation
VO_2	systemic oxygen demand

Publications

(full papers)

Colpaert C, Vermeulen P, van Beest P, Jeuris W, Goovaerts G, Weyler J, Van Dam P, Dirix L, Van Marck E: **Early distant relapse in 'node-negative' breast cancer patients is not predicted by occult axillary lymph node metastases, but the features of the primary tumor.** *J Pathol* 2001, 193(4): 442-449.

Colpaert C, Vermeulen P, van Beest P, Goovaerts G, Weyler J, Van Dam P, Dirix L, Van Marck E: **Intratumoural hypoxia resulting in the presence of a fibrotic focus is an independent predictor of early distant relapse in lymph node negative breast cancer patients**. *Histopathology* 2001, 39: 416-425.

Colpaert C, Vermeulen P, Benoy I, Soubry A, Van Roy F, van Beest P, Goovaerts G, Dirix L, Van Dam P, Fox S, Harris A, Van Marck E: **Inflammatory breast cancer shows angiogenesis with high endothelial proliferation rate and strong E-cadherin expression.** *Br J Cancer* 2003*,* **88**: 718-25.

Colpaert C, Vermeulen P, Lachaert R, van Beest P, Goovaerts G, Dirix L, Van Marck E: **Cutaneous breast cancer deposits show distinct growth patterns with different degrees of angiogenesis and fibrin deposition**. *Histopathology* 2003*,* **42**: 530-540.

van Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk P, Kuiper MA: **The incidence of low venous oxygen saturation on admission in the ICU: a multicenter observational study in the Netherlands**. *Crit Care* 2008, **12**: R33

van Beest PA, Kuiper MA: **Interpretatie van centraal of gemengd veneuze saturatie en rechter ventrikel ejectie fractie op de intensive care**. *Congresboek Venticare* 2009: 133-143.

van Beest PA, Mulder PJ, Bambang Oetomo S, van den Broek B, Kuiper MA, Spronk PE: **Measurement of lactate in a prehospital is related to outcome**. *Eur J Emerg Med* 2009, **16 (6)**: 318-322.

van Beest PA, van Ingen J, Boerma EC, Holman ND, Groen H, Koopmans M, Spronk PE, Kuiper MA: **Relation between mixed venous and central venous saturation in sepsis: no influence of sepsis origin**. *Crit Care* 2010, **14**: 219.

van Beest PA, Wietasch JKG, Scheeren TWL, Spronk PE, Kuiper MA: **The use of venous oxygen saturations as a goal: a yet unfinished puzzle. A clinical review**. *Crit Care* 2011, **15:** 232.

van Beest PA, Spronk PE: **Vroegtijdige doelgerichte therapie**; hoofdstuk 13; *Handboek Multiorgaanfalen*, eerste druk 2012; red. Groeneveld ABJ, Schultz MJ, Vroom MB; uitgeverij De Tijdstroom.

van Beest PA, van der Schors A, Liefers H, Coenen LGJ, Braam RL, Habib N, Braber A, Scheeren TWL, Kuiper MA, Spronk PE: **Femoral venous oxygen saturation is no surrogate for central venous oxygen saturation**. *Crit Care Med 2012, accepted*.

van Beest PA, Brander L, Jansen SPA, Rommes JH, Kuiper MA, Spronk PE: **Cumulative lactate in ICU patients: magnitude matters.** *2012, submitted*.

van Beest PA, Lont M, Holman N, Loef B, Kuiper MA, Boerma EC: **Veno-arterial PCO_2 difference as a tool in resuscitation of septic patients: time matters.** *2012, submitted*.

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